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(54) Title: RNA INTERFERENCE MEDIATED INHIBITION OF SEVERE ACUTE RESPIRATORY SYNDROME (SARS)
VIRUS GENE EXPRESSION USING SHORT INTERFERING NUCLEIC ACID (siNA)

(57) Abstract: The present invention comprises compounds, compositions, and methods useful for modulating the expression of
genes associated with respiratory and pulmonary disease, such as severe acute respiratory syndrome (SARS) virus genes, using short
interfering nucleic acid (siNA) molecules. This invention also comprises compounds, compositions, and methods useful for modu-
lating the expression and activity of SARS virus genes, or other genes involved in pathways of SARS virus gene expression and/or
activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic
acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), mi-
cro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of SARS virus RNA.



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**RNA INTERFERENCE MEDIATED INHIBITION OF SEVERE ACUTE
RESPIRATORY SYNDROME (SARS) VIRUS GENE EXPRESSION USING
SHORT INTERFERING NUCLEIC ACID (siNA)**

24/pds

This application claims the benefit of U.S. Provisional Application No. 5 60/462,874, filed April 15, 2003, and is a continuation-in-part of U.S. Patent Application No. 10/757,803, filed January 14, 2004, which is a continuation-in-part of U.S. Patent Application No. 10/720,448, filed November 24, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/693,059, filed October 23, 2003, which is a continuation-in-part of U.S. Patent Application No. 10/444,853, filed May 23, 2003. This application 10 is also a continuation-in-part of US Patent Application No. 10/427,160, filed April 30, 2003.

Reference is made to International Patent Application No. PCT/US03/05346, filed February 20, 2003, and International Patent Application No. PCT/US03/05028, filed February 20, 2003, both of which claim the benefit of U.S. Provisional Application No. 15 60/358,580 filed February 20, 2002, U.S. Provisional Application No. 60/363,124 filed March 11, 2002, U.S. Provisional Application No. 60/386,782 filed June 6, 2002, U.S. Provisional Application No. 60/406,784 filed August 29, 2002, U.S. Provisional Application No. 60/408,378 filed September 5, 2002, U.S. Provisional Application No. 60/409,293 filed September 9, 2002, and U.S. Provisional Application No. 60/440,129 20 filed January 15, 2003. Reference is also made to International Patent Application No. PCT/US02/15876 filed May 17, 2002.

All the listed applications are hereby incorporated by reference herein in their entireties, including the drawings.

Field Of The Invention

25 The present invention concerns compounds, compositions, and methods for the study, diagnosis, and treatment of diseases and conditions that respond to the modulation of severe acute respiratory syndrome (SARS) associated coronavirus (SARS virus) gene expression and/or activity. The present invention also concerns compounds, compositions, and methods relating to conditions and diseases that respond to the 30 modulation of expression and/or activity of genes involved in SARS virus pathways of

gene expression, including cellular genes that are involved in SARS virus infection. Specifically, the invention comprises small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules capable of
5 mediating RNA interference (RNAi) against severe acute respiratory syndrome (SARS) associated coronavirus gene expression.

Background Of The Invention

The following is a discussion of relevant art pertaining to RNAi. The discussion is provided only for understanding of the invention that follows. The summary is not an
10 admission that any of the work described below is prior art to the claimed invention.

RNA interference refers to the process of sequence-specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, *Cell*, 101, 25-33; Fire *et al.*, 1998, *Nature*, 391, 806; Hamilton *et al.*, 1999, *Science*, 286, 950-951; Lin *et al.*, 1999, *Nature*, 402, 128-129; Sharp, 1999, *Genes &*
15 *Dev.*, 13:139-141; and Strauss, 1999, *Science*, 286, 886). The corresponding process in plants (Heifetz *et al.*, International PCT Publication No. WO 99/61631) is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression
20 of foreign genes and is commonly shared by diverse flora and phyla (Fire *et al.*, 1999, *Trends Genet.*, 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or from the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or
25 viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response through a mechanism that has yet to be fully characterized. This mechanism appears to be different from other known mechanisms involving double stranded RNA-specific ribonucleases, such as the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2',5'-oligoadenylate synthetase resulting in non-
30 specific cleavage of mRNA by ribonuclease L (see for example US Patent Nos.

6,107,094; 5,898,031; Clemens *et al.*, 1997, *J. Interferon & Cytokine Res.*, 17, 503-524; Adah *et al.*, 2001, *Curr. Med. Chem.*, 8, 1189).

The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as dicer (Bass, 2000, *Cell*, 101, 235; Zamore *et al.*, 2000, *Cell*, 101, 25-33; Hammond *et al.*, 2000, *Nature*, 404, 293). Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Zamore *et al.*, 2000, *Cell*, 101, 25-33; Bass, 2000, *Cell*, 101, 235; Bernstein *et al.*, 2001, *Nature*, 409, 363). Short interfering RNAs derived from dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes (Zamore *et al.*, 2000, *Cell*, 101, 25-33; Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188). Dicer has also been implicated in the excision of 21 and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.*, 2001, *Science*, 293, 834). The RNAi response also features an endonuclease complex, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded RNA having sequence complementary to the antisense strand of the siRNA duplex. Cleavage of the target RNA takes place in the middle of the region complementary to the antisense strand of the siRNA duplex (Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188).

RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature*, 391, 806, were the first to observe RNAi in *C. elegans*. Bahramian and Zarbl, 1999, *Molecular and Cellular Biology*, 19, 274-283 and Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mammalian systems. Hammond *et al.*, 2000, *Nature*, 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA. Elbashir *et al.*, 2001, *Nature*, 411, 494 and Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in *Drosophila* embryonic lysates (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877 and Tuschl *et al.*, International PCT Publication No. WO 01/75164) has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown that 21-nucleotide siRNA duplexes are most active when containing 3'-terminal dinucleotide

overhangs. Furthermore, complete substitution of one or both siRNA strands with 2'-deoxy (2'-H) or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of the 3'-terminal siRNA overhang nucleotides with 2'-deoxy nucleotides (2'-H) was shown to be tolerated. Single mismatch sequences in the center of the siRNA duplex were also
5 shown to abolish RNAi activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end of the guide sequence (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to
10 maintain the 5'-phosphate moiety on the siRNA (Nykanen *et al.*, 2001, *Cell*, 107, 309).

Studies have shown that replacing the 3'-terminal nucleotide overhanging segments of a 21-mer siRNA duplex having two-nucleotide 3'-overhangs with deoxyribonucleotides does not have an adverse effect on RNAi activity. Replacing up to four nucleotides on each end of the siRNA with deoxyribonucleotides has been reported
15 to be well tolerated, whereas complete substitution with deoxyribonucleotides results in no RNAi activity (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877 and Tuschl *et al.*, International PCT Publication No. WO 01/75164). In addition, Elbashir *et al.*, *supra*, also report that substitution of siRNA with 2'-O-methyl nucleotides completely abolishes RNAi activity. Li *et al.*, International PCT Publication No. WO 00/44914, and Beach *et al.*,
20 *International PCT Publication No. WO 01/68836* preliminarily suggest that siRNA may include modifications to either the phosphate-sugar backbone or the nucleoside to include at least one of a nitrogen or sulfur heteroatom, however, neither application postulates to what extent such modifications would be tolerated in siRNA molecules, nor provides any further guidance or examples of such modified siRNA. Kreutzer *et al.*,
25 Canadian Patent Application No. 2,359,180, also describe certain chemical modifications for use in dsRNA constructs in order to counteract activation of double-stranded RNA-dependent protein kinase PKR, specifically 2'-amino or 2'-O-methyl nucleotides, and nucleotides containing a 2'-O or 4'-C methylene bridge. However, Kreutzer *et al.* similarly fails to provide examples or guidance as to what extent these modifications
30 would be tolerated in dsRNA molecules.

Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, tested certain chemical modifications targeting the *unc-22* gene in *C. elegans* using long (>25 nt) siRNA transcripts. The authors describe the introduction of thiophosphate residues into these siRNA transcripts by incorporating thiophosphate nucleotide analogs with T7 and T3 RNA polymerase and observed that RNAs with two phosphorothioate modified bases also had substantial decreases in effectiveness as RNAi. Further, Parrish *et al.* reported that phosphorothioate modification of more than two residues greatly destabilized the RNAs *in vitro* such that interference activities could not be assayed. *Id.* at 1081. The authors also tested certain modifications at the 2'-position of the nucleotide sugar in the long siRNA transcripts and found that substituting deoxynucleotides for ribonucleotides produced a substantial decrease in interference activity, especially in the case of Uridine to Thymidine and/or Cytidine to deoxy-Cytidine substitutions. *Id.* In addition, the authors tested certain base modifications, including substituting, in sense and antisense strands of the siRNA, 4-thiouracil, 5-bromouracil, 5-iodouracil, and 3-(aminoallyl)uracil for uracil, and inosine for guanosine. Whereas 4-thiouracil and 5-bromouracil substitution appeared to be tolerated, Parrish reported that inosine produced a substantial decrease in interference activity when incorporated in either strand. Parrish also reported that incorporation of 5-iodouracil and 3-(aminoallyl)uracil in the antisense strand resulted in a substantial decrease in RNAi activity as well.

The use of longer dsRNA has been described. For example, Beach *et al.*, International PCT Publication No. WO 01/68836, describes specific methods for attenuating gene expression using endogenously-derived dsRNA. Tuschl *et al.*, International PCT Publication No. WO 01/75164, describe a *Drosophila in vitro* RNAi system and the use of specific siRNA molecules for certain functional genomic and certain therapeutic applications; although Tuschl, 2001, *Chem. Biochem.*, 2, 239-245, doubts that RNAi can be used to cure genetic diseases or viral infection due to the danger of activating interferon response. Li *et al.*, International PCT Publication No. WO 00/44914, describe the use of specific long (141 bp-488 bp) enzymatically synthesized or vector expressed dsRNAs for attenuating the expression of certain target genes. Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646, describe certain methods for inhibiting the expression of particular genes in mammalian cells using certain long (550 bp-714 bp), enzymatically synthesized or vector expressed dsRNA

molecules. Fire *et al.*, International PCT Publication No. WO 99/32619, describe particular methods for introducing certain long dsRNA molecules into cells for use in inhibiting gene expression in nematodes. Plaetinck *et al.*, International PCT Publication No. WO 00/01846, describe certain methods for identifying specific genes responsible for conferring a particular phenotype in a cell using specific long dsRNA molecules. Mello *et al.*, International PCT Publication No. WO 01/29058, describe the identification of specific genes involved in dsRNA-mediated RNAi. Pachuck *et al.*, International PCT Publication No. WO 00/63364, describe certain long (at least 200 nucleotide) dsRNA constructs. Deschamps Depaillette *et al.*, International PCT Publication No. WO 99/07409, describe specific compositions consisting of particular dsRNA molecules combined with certain anti-viral agents. Waterhouse *et al.*, International PCT Publication No. 99/53050 and 1998, *PNAS*, 95, 13959-13964, describe certain methods for decreasing the phenotypic expression of a nucleic acid in plant cells using certain dsRNAs. Driscoll *et al.*, International PCT Publication No. WO 01/49844, describe specific DNA expression constructs for use in facilitating gene silencing in targeted organisms.

Others have reported on various RNAi and gene-silencing systems. For example, Parrish *et al.*, 2000, *Molecular Cell*, 6, 1077-1087, describe specific chemically-modified dsRNA constructs targeting the *unc-22* gene of *C. elegans*. Grossniklaus, International PCT Publication No. WO 01/38551, describes certain methods for regulating polycomb gene expression in plants using certain dsRNAs. Churikov *et al.*, International PCT Publication No. WO 01/42443, describe certain methods for modifying genetic characteristics of an organism using certain dsRNAs. Cogoni *et al.*, International PCT Publication No. WO 01/53475, describe certain methods for isolating a *Neurospora* silencing gene and uses thereof. Reed *et al.*, International PCT Publication No. WO 01/68836, describe certain methods for gene silencing in plants. Honer *et al.*, International PCT Publication No. WO 01/70944, describe certain methods of drug screening using transgenic nematodes as Parkinson's Disease models using certain dsRNAs. Deak *et al.*, International PCT Publication No. WO 01/72774, describe certain *Drosophila*-derived gene products that may be related to RNAi in *Drosophila*. Arndt *et al.*, International PCT Publication No. WO 01/92513 describe certain methods for mediating gene suppression by using factors that enhance RNAi. Tuschl *et al.*,

International PCT Publication No. WO 02/44321, describe certain synthetic siRNA constructs. Pachuk *et al.*, International PCT Publication No. WO 00/63364, and Satishchandran *et al.*, International PCT Publication No. WO 01/04313, describe certain methods and compositions for inhibiting the function of certain polynucleotide sequences using certain long (over 250 bp), vector expressed dsRNAs. Echeverri *et al.*, International PCT Publication No. WO 02/38805, describe certain *C. elegans* genes identified via RNAi. Kreutzer *et al.* International PCT Publications Nos. WO 02/055692, WO 02/055693, and EP 1144623 B1 describes certain methods for inhibiting gene expression using dsRNA. Graham *et al.*, International PCT Publications Nos. WO 99/49029 and WO 01/70949, and AU 4037501 describe certain vector expressed siRNA molecules. Fire *et al.*, US 6,506,559, describe certain methods for inhibiting gene expression in vitro using certain long dsRNA (299 bp-1033 bp) constructs that mediate RNAi. Martinez *et al.*, 2002, *Cell*, 110, 563-574, describe certain single stranded siRNA constructs, including certain 5'-phosphorylated single stranded siRNAs that mediate RNA interference in Hela cells. Harborth *et al.*, 2003, *Antisense & Nucleic Acid Drug Development*, 13, 83-105, describe certain chemically and structurally modified siRNA molecules. Chiu and Rana, 2003, *RNA*, 9, 1034-1048, describe certain chemically and structurally modified siRNA molecules.

McCaffrey *et al.*, 2002, *Nature*, 418, 38-39, describes the use of certain siRNA constructs targeting a chimeric SARS NS5B protein/luciferase transcript in mice.

Randall *et al.*, 2003, *PNAS USA*, 100, 235-240, describe certain siRNA constructs targeting SARS RNA in Huh7 hepatoma cell lines.

SUMMARY OF THE INVENTION

This invention comprises compounds, compositions, and methods useful for modulating the expression of genes associated with the development or maintenance of SARS virus infection, acute respiratory failure, viral pneumonia, and/or other disease states associated with SARS virus infection,, using short interfering nucleic acid (siNA) molecules. This invention also comprises compounds, compositions, and methods useful

for modulating the expression and activity of severe acute respiratory syndrome (SARS) associated coronavirus or genes involved in severe acute respiratory syndrome (SARS) associated coronavirus gene expression and/or activity by RNA interference (RNAi) using small nucleic acid molecules. In particular, the instant invention features small nucleic acid molecules, such as short interfering nucleic acid (siNA), short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), and short hairpin RNA (shRNA) molecules and methods used to modulate the expression of severe acute respiratory syndrome (SARS) associated coronavirus. For convenience, all forms of the small nucleic acid molecules of the invention (*e.g.*, siRNA, dsRNA, micro-RNA, etc.) are referred to herein as "siNA," unless expressly stated otherwise.

A siNA of the invention can be unmodified or chemically-modified. A siNA of the instant invention can be chemically synthesized, expressed from a vector or enzymatically synthesized. The instant invention also features various chemically-modified synthetic short interfering nucleic acid (siNA) molecules capable of modulating repeat expansion gene expression or activity in cells by RNA interference (RNAi). The use of chemically-modified siNA improves various properties of native siNA molecules through increased resistance to nuclease degradation *in vivo* and/or through improved cellular uptake. Further, contrary to earlier published studies, siNA having multiple chemical modifications retains its RNAi activity. The siNA molecules of the instant invention are useful reagents and are useful in methods for a variety of therapeutic, diagnostic, target validation, genomic discovery, genetic engineering, and pharmacogenomic applications.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of gene(s) encoding SARS virus. Specifically, the present invention comprises siNA molecules that modulate the expression of SARS proteins, for example, proteins encoded by SARS virus genome, such as Genbank Accession Nos. in Table I.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of genes representing cellular targets for SARS virus infection, such as cellular receptors,

cell surface molecules, cellular enzymes, cellular transcription factors, and/or cytokines, second messengers, and cellular accessory molecules.

Due to the high sequence variability of the SARS genome, selection of siNA molecules for broad therapeutic applications preferably involve the conserved regions of the SARS genome. In one embodiment, the present invention comprises siNA molecules that target the conserved regions of the SARS genome, such as the polymerase encoding region of the SARS virus genomic RNA. Therefore, siNA molecules of the invention are designed to target all the different isolates of SARS. siNA molecules designed to target conserved regions of various SARS isolates enable efficient inhibition of SARS replication in diverse patient populations and ensure the effectiveness of the siNA molecules against SARS quasi species that evolve due to mutations in the non-conserved regions of the SARS genome. Therefore, a single siNA molecule can be targeted against all isolates of SARS by designing the siNA molecule to interact with conserved nucleotide sequences of SARS (such conserved sequences are expected to be present in the RNA of all SARS isolates).

In one embodiment, a siNA molecule is designed to target the 3'-untranslated region and/or the shared leader sequence of genomic SARS RNA transcripts. Because SARS coronavirus mRNAs are nested with the genomic RNA and share common 3' region and polyA region, a single siNA targeting the 3'-end can target all transcripts plus the genomic RNA.

In one embodiment, a siNA molecule of the invention targets both the plus (genomic) strand RNA and minus strand RNA of the SARS virus. Because the SARS virus generates a minus strand RNA from plus strand genomic RNA, a double stranded siNA molecule targeting the plus strand will also target the minus strand, thus allowing a single double-stranded siNA to target both the plus (genomic) and the minus strand of the SARS virus. For example, a double stranded siNA molecule targeting the 3'-end of the SARS virus genomic strand will also target the 3'-end of the the minus strand, thus allowing a single double-stranded siNA to target both the plus and the minus strand of the SARS virus.

In one embodiment, the invention comprises one or more siNA molecules (and methods of using them) that independently or in combination modulate the expression of gene(s) encoding SARS virus and/or cellular proteins associated with the maintenance or development of SARS virus infection and/or acute respiratory failure, viral pneumonia, such as genes encoding sequences comprising those sequences referred to by GenBank Accession Nos. shown in Table I, referred to herein generally as SARS. The description below of the various aspects and embodiments of the invention is provided with reference to exemplary severe acute respiratory syndrome (SARS) associated coronavirus genes, generally referred to herein as SARS. However, such reference is meant to be exemplary only and the various aspects and embodiments of the invention are also directed to other genes that express alternate SARS genes, such as mutant SARS genes, splice variants of SARS genes, and genes encoding different strains of SARS, as well as as cellular targets for SARS, such as those described herein. The various aspects and embodiments are also directed to other genes involved in SARS pathways, including genes that encode cellular proteins involved in the maintenance and/or development of SARS virus infection and/or acute respiratory failure or other genes that express other proteins associated with SARS virus infection, such as cellular proteins that are utilized in the SARS life-cycle. Such additional genes can be analyzed for target sites using the methods described herein for SARS. Thus, the inhibition and the effects of such inhibition of the other genes can be performed as described herein. In other words, the term "SARS" as it is defined herein below and recited in the described embodiments, is meant to encompass genes associated with the development or maintenance of SARS virus infection, such as genes which encode SARS polypeptides, including polypeptides of different strains of SARS, mutant SARS genes, and splice variants of SARS genes, as well as cellular genes involved in SARS pathways of gene expression, replication, and/or SARS activity. Also, the term "SARS" as it is defined herein and recited in the described embodiments, is meant to encompass SARS viral gene products and cellular gene products involved in SARS virus infection, such as those described herein. Thus, each of the embodiments described herein with reference to the term "SARS" are applicable to all of the virus, cellular and viral protein, peptide, polypeptide, and/or polynucleotide molecules covered by the term "SARS" as that term is defined herein.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a severe acute respiratory syndrome virus (e.g., SARS) gene, wherein said siNA molecule comprises about 19 to about 23 base pairs. Preferably the number of based pairs in the siNA molecule is 18, 19, 20, 21, 22, 23, or 24.

In one embodiment, the invention features a siNA molecule that down-regulates expression of a SARS gene, for example, wherein the SARS gene comprises SARS encoding sequence. In one embodiment, the invention features a siNA molecule that down-regulates expression of a SARS gene, for example, wherein the SARS gene comprises SARS non-coding sequence or regulatory elements involved in SARS gene expression.

In one embodiment, the invention features a siNA molecule having RNAi activity against SARS RNA, wherein the siNA molecule comprises a sequence complementary to any RNA having SARS encoding sequence, such as those sequences having GenBank Accession Nos. shown in **Table I**. In another embodiment, the invention features a siNA molecule having RNAi activity against SARS RNA, wherein the siNA molecule comprises a sequence complementary to an RNA having other SARS encoding sequence, for example other mutant SARS genes not shown in **Table I** but known in the art to be associated with respiratory and/or pulmonary disease, SARS virus infection and/or acute respiratory failure, viral pneumonia, impeded respiration, respiratory distress syndrome, pulmonary hypertension, or pulmonary vasoconstriction. Chemical modifications as shown in **Tables III and IV** or otherwise described herein can be applied to any siNA construct of the invention. In another embodiment, a siNA molecule of the invention includes nucleotide sequence that can interact with nucleotide sequence of a SARS gene and thereby mediate silencing of SARS gene expression, for example, wherein the siNA mediates regulation of SARS gene expression by cellular processes that modulate the chromatin structure of the SARS gene and prevent transcription of the SARS gene.

In another embodiment, the invention features a siNA molecule comprising nucleotide sequence, for example, nucleotide sequence in the antisense region of the siNA molecule that is complementary to a nucleotide sequence or portion of sequence of

a SARS gene. In another embodiment, the invention features a siNA molecule comprising a region, for example, the antisense region of the siNA construct, complementary to a sequence comprising a SARS gene sequence or a portion thereof.

In one embodiment, the antisense region of SARS siNA constructs can comprise a
5 sequence complementary to sequence having any of SEQ ID NOs. 1-1651 or 3303-3318. In one embodiment, the antisense region can also comprise sequence having any of SEQ ID NOs. 1652-3302, 3319-3326, 3335-3342, 3351-3358, 3367-3374, 3376, 3378, 3380, 3383, 3385, 3387, 3389, or 3392. In another embodiment, the sense region of the SARS constructs can comprise sequence having any of SEQ ID NOs. 1-1651, 3303-3310, 3311-
10 3318, 3327-3334, 3343-3350, 3359-3366, 3375, 3377, 3379, 3381, 3382, 3384, 3386, 3388, 3390, or 3391.

In one embodiment, a siNA molecule of the invention comprises any of SEQ ID NOs. 1-3392. The sequences shown in SEQ ID NOs: 1-3392 are not limiting. A siNA molecule of the invention can comprise any contiguous SARS sequence (e.g., about 19
15 to about 25, or about 19, 20, 21, 22, 23, 24 or 25 contiguous SARS nucleotides).

In yet another embodiment, the invention features a siNA molecule comprising a sequence, for example, the antisense sequence of the siNA construct, complementary to a sequence or portion of sequence comprising sequence represented by GenBank Accession Nos. shown in **Table I**. Chemical modifications in **Tables III and IV** and
20 described herein can be applied to any siNA construct of the invention. siNA molecules of the invention are unmodified or have up to all nucleotides modified with modifications according to Tables III and IV.

In one embodiment of the invention a siNA molecule comprises an antisense strand having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or
25 30) nucleotides, wherein the antisense strand is complementary to a RNA sequence encoding a SARS protein, and wherein said siNA further comprises a sense strand having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, and wherein said sense strand and said antisense strand are distinct nucleotide sequences with at least about 19 complementary nucleotides.

In another embodiment of the invention a siNA molecule of the invention comprises an antisense region having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30) nucleotides, wherein the antisense region is complementary to a RNA sequence encoding a SARS protein, and wherein said siNA further comprises a
5 sense region having about 19 to about 29 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more) nucleotides, wherein said sense region and said antisense region comprise a linear molecule with at least about 19 complementary nucleotides.

In one embodiment of the invention a siNA molecule comprises an antisense strand comprising a nucleotide sequence that is complementary to a nucleotide sequence
10 or a portion thereof encoding a SARS protein. The siNA further comprises a sense strand, wherein said sense strand comprises a nucleotide sequence of a SARS gene or a portion thereof.

In another embodiment, a siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence
15 encoding a SARS protein or a portion thereof. The siNA molecule further comprises a sense region, wherein said sense region comprises a nucleotide sequence of a SARS gene or a portion thereof.

In one embodiment, a siNA molecule of the invention has RNAi activity that modulates expression of RNA encoded by a SARS gene. Because SARS genes can
20 share some degree of sequence homology with each other, siNA molecules can be designed to target a class of SARS genes or alternately specific SARS genes by selecting sequences that are either shared among different SARS targets (e.g., different viral strains) or alternatively that are unique for a specific SARS target (e.g., a particular viral strain). Therefore, in one embodiment, the siNA molecule can be designed to target
25 conserved regions of SARS RNA sequences having homology among several SARS genes so as to target several SARS genes (e.g., different SARS isoforms, splice variants, mutant genes etc.) with one siNA molecule. In another embodiment, the siNA molecule can be designed to target a sequence that is unique to a specific SARS RNA sequence due to the high degree of specificity that the siNA molecule requires to mediate RNAi
30 activity.

In one embodiment, nucleic acid molecules of the invention that act as mediators of the RNA interference gene silencing response are double-stranded nucleic acid molecules. In another embodiment, the siNA molecules of the invention consist of duplexes containing about 19 base pairs between oligonucleotides comprising about 19
5 to about 25 (e.g., 18, 19, 20, 21, 22, 23, 24, 25, or 26) nucleotides. In yet another embodiment, siNA molecules of the invention comprise duplexes with overhanging ends of about about 1 to about 3 (e.g., 1, 2, 3, or 4) nucleotides, for example, about 21-nucleotide duplexes with about 19 base pairs and 3'-terminal mononucleotide, dinucleotide, or trinucleotide overhangs.

10 In one embodiment, the invention features one or more chemically-modified siNA constructs having specificity for SARS expressing nucleic acid molecules, such as RNA encoding a SARS protein. Non-limiting examples of such chemical modifications include without limitation phosphorothioate internucleotide linkages, 2'-deoxyribonucleotides, 2'-O-methyl ribonucleotides, 2'-deoxy-2'-fluoro ribonucleotides,
15 "universal base" nucleotides, "acyclic" nucleotides, 5-C-methyl nucleotides, and terminal glyceryl and/or inverted deoxy abasic residue incorporation. These chemical modifications, when used in various siNA constructs, are shown to preserve RNAi activity in cells while at the same time, dramatically increasing the serum stability of these compounds. Furthermore, contrary to the data published by Parrish *et al.*, *supra*,
20 applicant demonstrates that multiple (greater than one) phosphorothioate substitutions are well-tolerated and confer substantial increases in serum stability for modified siNA constructs.

In one embodiment, a siNA molecule of the invention comprises modified nucleotides while maintaining the ability to mediate RNAi. The modified nucleotides
25 can be used to improve *in vitro* or *in vivo* characteristics such as stability, activity, and/or bioavailability. For example, a siNA molecule of the invention can comprise modified nucleotides as a percentage of the total number of nucleotides present in the siNA molecule. As such, a siNA molecule of the invention can generally comprise about 5% to about 100% modified nucleotides (e.g., 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%,
30 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% modified nucleotides). The actual percentage of modified nucleotides present in a given siNA

molecule will depend on the total number of nucleotides present in the siNA. If the siNA molecule is single stranded, the percent modification can be based upon the total number of nucleotides present in the single stranded siNA molecules. Likewise, if the siNA molecule is double stranded, the percent modification can be based upon the total
5 number of nucleotides present in the sense strand, antisense strand, or both the sense and antisense strands.

One aspect of the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene. In one embodiment, a double stranded siNA molecule comprises one or more chemical
10 modifications and each strand of the double-stranded siNA is about 21 nucleotides long. In one embodiment, the double-stranded siNA molecule does not contain any ribonucleotides. In another embodiment, the double-stranded siNA molecule comprises one or more ribonucleotides. In one embodiment, each strand of the double-stranded siNA molecule comprises about 19 to about 23 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26,
15 27, 28, or 29) nucleotides, wherein each strand comprises about 19 nucleotides that are complementary to the nucleotides of the other strand. In one embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence or a portion thereof of the SARS gene, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence
20 substantially similar to the nucleotide sequence of the SARS gene or a portion thereof.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of the SARS gene or a portion
25 thereof, and a sense region, wherein the sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of the SARS gene or a portion thereof. In one embodiment, the antisense region and the sense region each comprise about 19 to about 23 (e.g. about 19, 20, 21, 22, or 23) nucleotides, wherein the antisense region comprises about 19 nucleotides that are complementary to nucleotides of the sense
30 region.

In another embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region.

In one embodiment, the SARS virus RNA contemplated by the invention comprises SARS virus minus strand RNA. In another embodiment, the SARS virus RNA contemplated by the invention comprises SARS virus plus strand RNA.

In one embodiment, a siNA molecule of the invention comprises blunt ends, i.e., ends that do not include any overhanging nucleotides. For example, a siNA molecule of the invention comprising modifications described herein (e.g., comprising nucleotides having Formulae I-VII or siNA constructs comprising Stab00-Stab22 or any combination thereof (see Table IV)) and/or any length described herein can comprise blunt ends or ends with no overhanging nucleotides.

In one embodiment, any siNA molecule of the invention can comprise one or more blunt ends, i.e., where a blunt end does not have any overhanging nucleotides. In a non-limiting example, a blunt ended siNA molecule has a number of base pairs equal to the number of nucleotides present in each strand of the siNA molecule. In another example, a siNA molecule comprises one blunt end, for example wherein the 5'-end of the antisense strand and the 3'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises one blunt end, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand do not have any overhanging nucleotides. In another example, a siNA molecule comprises two blunt ends, for example wherein the 3'-end of the antisense strand and the 5'-end of the sense strand as well as the 5'-end of the antisense strand and 3'-end of the sense strand do not have any overhanging nucleotides. A blunt ended siNA molecule can comprise, for example, from about 18 to about 30 nucleotides (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides). Other nucleotides present in a blunt ended siNA molecule can comprise mismatches, bulges, loops, or wobble base pairs, for example, to modulate the activity of the siNA molecule to mediate RNA interference.

By "blunt ends" is meant symmetric termini or termini of a double stranded siNA molecule having no overhanging nucleotides. The two strands of a double stranded siNA molecule align with each other without over-hanging nucleotides at the termini. For example, a blunt ended siNA construct comprises terminal nucleotides that are
5 complementary between the sense and antisense regions of the siNA molecule.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the
10 antisense region of the siNA molecule. The sense region can be connected to the antisense region via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker.

In one embodiment, the invention features double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein
15 the siNA molecule comprises about 19 to about 21 base pairs, and wherein each strand of the siNA molecule comprises one or more chemical modifications. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a
20 nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of the SARS gene. In another embodiment, one of the strands of the double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the second strand of the double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the
25 nucleotide sequence or a portion thereof of the SARS gene. In another embodiment, each strand of the siNA molecule comprises about 19 to about 23 nucleotides, and each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, a siNA molecule of the invention comprises no ribonucleotides. In another embodiment, a siNA molecule of the invention comprises ribonucleotides.

5 In one embodiment, a siNA molecule of the invention comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a SARS gene or a portion thereof, and the siNA further comprises a sense region comprising a nucleotide sequence substantially similar to the nucleotide sequence of the SARS gene or a portion thereof. In another embodiment, the antisense region and the sense region each comprise about 19 to about 23 nucleotides and the antisense region
10 comprises at least about 19 nucleotides that are complementary to nucleotides of the sense region. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, a siNA molecule of the invention comprises a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by a SARS gene, or a
15 portion thereof, and the sense region comprises a nucleotide sequence that is complementary to the antisense region. In another embodiment, the siNA molecule is assembled from two separate oligonucleotide fragments, wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment, the sense region is connected to the
20 antisense region via a linker molecule. In another embodiment, the sense region is connected to the antisense region via a linker molecule, such as a nucleotide or non-nucleotide linker. The SARS gene can comprise, for example, sequences referred to Table I.

In one embodiment, the invention features a double-stranded short interfering
25 nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a nucleotide sequence that is complementary to the antisense region, and wherein the siNA
30 molecule has one or more modified pyrimidine and/or purine nucleotides. In one embodiment, the pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine

nucleotides or 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides.

5 In another embodiment, the pyrimidine nucleotides in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-deoxy purine nucleotides. In one embodiment, the pyrimidine nucleotides in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the antisense region are 2'-O-methyl or 2'-deoxy purine nucleotides. In

10 another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the sense strand (e.g. overhang region) are 2'-deoxy nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein

15 the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule, and wherein the fragment comprising the sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment. In another embodiment, the terminal cap moiety is an inverted

20 deoxy abasic moiety or glyceryl moiety. In another embodiment, each of the two fragments of the siNA molecule comprise about 21 nucleotides.

In one embodiment, the invention features a siNA molecule comprising at least one modified nucleotide, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. The siNA can be, for example, of length between about 12 and about 36 nucleotides. In

25 another embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In another embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In another

30 embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all cytidine nucleotides present in the siNA are 2'-

deoxy-2'-fluoro cytidine nucleotides. In another embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In another embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified
5 internucleotidic linkage, such as phosphorothioate linkage. In another embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a method of increasing the stability of a
10 siNA molecule against cleavage by ribonucleases comprising introducing at least one modified nucleotide into the siNA molecule, wherein the modified nucleotide is a 2'-deoxy-2'-fluoro nucleotide. In another embodiment, all pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides. In another embodiment, the modified nucleotides in the siNA include at least one 2'-deoxy-2'-fluoro cytidine or 2'-
15 deoxy-2'-fluoro uridine nucleotide. In another embodiment, the modified nucleotides in the siNA include at least one 2'-fluoro cytidine and at least one 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all uridine nucleotides present in the siNA are 2'-deoxy-2'-fluoro uridine nucleotides. In another embodiment, all cytidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro cytidine nucleotides. In another
20 embodiment, all adenosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro adenosine nucleotides. In another embodiment, all guanosine nucleotides present in the siNA are 2'-deoxy-2'-fluoro guanosine nucleotides. The siNA can further comprise at least one modified internucleotidic linkage, such as phosphorothioate linkage. In another embodiment, the 2'-deoxy-2'-fluoronucleotides are present at specifically selected
25 locations in the siNA that are sensitive to cleavage by ribonucleases, such as locations having pyrimidine nucleotides.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene comprising a sense region and an antisense region, wherein the antisense region
30 comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by the SARS gene or a portion thereof and the sense region comprises a

nucleotide sequence that is complementary to the antisense region, and wherein the purine nucleotides present in the antisense region comprise 2'-deoxy- purine nucleotides. In an alternative embodiment, the purine nucleotides present in the antisense region comprise 2'-O-methyl purine nucleotides. In either of the above embodiments, the antisense region can comprise a phosphorothioate internucleotide linkage at the 3' end of the antisense region. Alternatively, in either of the above embodiments, the antisense region can comprise a glyceryl modification at the 3' end of the antisense region. In another embodiment of any of the above-described siNA molecules, any nucleotides present in a non-complementary region of the antisense strand (e.g. overhang region) are 2'-deoxy nucleotides.

In one embodiment, the antisense region of a siNA molecule of the invention comprises sequence complementary to a portion of a SARS transcript having sequence unique to a particular SARS disease related allele, such as sequence comprising a SNP associated with the disease specific allele. As such, the antisense region of a siNA molecule of the invention can comprise sequence complementary to sequences that are unique to a particular allele to provide specificity in mediating selective RNAi against the disease related allele.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that down-regulates expression of a SARS gene, wherein the siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and the second fragment comprises the antisense region of the siNA molecule. In another embodiment about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other fragment of the siNA molecule. In one embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine nucleotide, such as a 2'-deoxy-thymidine. In another embodiment, all 21 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule. In another embodiment, about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the

RNA encoded by the SARS gene. In another embodiment, about 21 nucleotides of the antisense region are base-paired to the nucleotide sequence or a portion thereof of the RNA encoded by the SARS gene. In any of the above embodiments, the 5'-end of the fragment comprising said antisense region can optionally includes a phosphate group.

- 5 In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits the expression of a SARS RNA sequence (e.g., wherein said target RNA sequence is encoded by a SARS gene involved in the SARS pathway), wherein the siNA molecule does not contain any ribonucleotides and wherein each strand of the double-stranded siNA molecule is about 21 nucleotides long.
- 10 Examples of non-ribonucleotide containing siNA constructs are combinations of stabilization chemistries shown in Table IV in any combination of Sense/Antisense chemistries, such as Stab 7/8, Stab 7/11, Stab 8/8, Stab 18/8, Stab 18/11, Stab 12/13, Stab 7/13, Stab 18/13, Stab 7/19, Stab 8/19, Stab 18/19, Stab 7/20, Stab 8/20, or Stab 18/20.
- 15 In one embodiment, the invention features a chemically synthesized double stranded RNA molecule that directs cleavage of a SARS RNA via RNA interference, wherein each strand of said RNA molecule is about 21 to about 23 nucleotides in length; one strand of the RNA molecule comprises nucleotide sequence having sufficient complementarity to the SARS RNA for the RNA molecule to direct cleavage of the
- 20 SARS RNA via RNA interference; and wherein at least one strand of the RNA molecule comprises one or more chemically modified nucleotides described herein, such as deoxynucleotides, 2'-O-methyl nucleotides, 2'-deoxy-2'-fluoro nucleotides, 2'-O-methoxyethyl nucleotides etc.

25 In one embodiment, the invention features a medicament comprising a siNA molecule of the invention.

 In one embodiment, the invention features an active ingredient comprising a siNA molecule of the invention.

 In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule to down-regulate expression of a SARS gene,

wherein the siNA molecule comprises one or more chemical modifications and each strand of the double-stranded siNA is about 18 to about 28 or more (e.g., 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or more) nucleotides long.

5 In one embodiment, the invention features the use of a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense
10 strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises
15 nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification.

20 In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA that encodes a protein or portion thereof, the other strand is a sense strand which comprises
25 nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded
30 siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other

strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification. In one embodiment, each strand of the siNA molecule comprises about 18
5 to about 29 or more (e.g., about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or more) nucleotides, wherein each strand comprises at least about 18 nucleotides that are complementary to the nucleotides of the other strand. In another embodiment, the siNA molecule is assembled from two oligonucleotide fragments, wherein one fragment comprises the nucleotide sequence of the antisense strand of the siNA molecule and a
10 second fragment comprises nucleotide sequence of the sense region of the siNA molecule. In yet another embodiment, the sense strand is connected to the antisense strand via a linker molecule, such as a polynucleotide linker or a non-nucleotide linker. In a further embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense
15 region are 2'-deoxy purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and the purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides. In still another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the
20 antisense strand are 2'-deoxy purine nucleotides. In another embodiment, the antisense strand comprises one or more 2'-deoxy-2'-fluoro pyrimidine nucleotides and one or more 2'-O-methyl purine nucleotides. In another embodiment, the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides and any purine nucleotides present in the antisense strand are 2'-O-methyl purine
25 nucleotides. In a further embodiment the sense strand comprises a 3'-end and a 5'-end, wherein a terminal cap moiety (e.g., an inverted deoxy abasic moiety or inverted deoxy nucleotide moiety such as inverted thymidine) is present at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand. In another embodiment, the antisense strand comprises a phosphorothioate internucleotide linkage at the 3' end of the antisense
30 strand. In another embodiment, the antisense strand comprises a glyceryl modification at the 3' end. In another embodiment, the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein each of the two strands of the siNA molecule comprises about 21 nucleotides. In one embodiment, about 21 nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 19 nucleotides of each strand of the siNA molecule are base-paired to the complementary nucleotides of the other strand of the siNA molecule, wherein at least two 3' terminal nucleotides of each strand of the siNA molecule are not base-paired to the nucleotides of the other strand of the siNA molecule. In another embodiment, each of the two 3' terminal nucleotides of each fragment of the siNA molecule is a 2'-deoxy-pyrimidine, such as 2'-deoxy-thymidine. In another embodiment, each strand of the siNA molecule is base-paired to the complementary nucleotides of the other strand of the siNA molecule. In another embodiment, about 19 nucleotides of the antisense strand are base-paired to the nucleotide sequence of the SARS RNA or a portion thereof. In another embodiment, about 21 nucleotides of the antisense strand are base-paired to the nucleotide sequence of the SARS RNA or a portion thereof.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the 5'-end of the antisense strand optionally includes a phosphate group.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand and wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence or a portion thereof of the antisense strand is complementary to a nucleotide sequence of the untranslated region or a portion thereof of the SARS RNA.

In one embodiment, the invention features a double-stranded short interfering nucleic acid (siNA) molecule that inhibits expression of a SARS gene, wherein one of the strands of the double-stranded siNA molecule is an antisense strand which comprises nucleotide sequence that is complementary to nucleotide sequence of SARS RNA or a portion thereof, wherein the other strand is a sense strand which comprises nucleotide sequence that is complementary to a nucleotide sequence of the antisense strand, wherein a majority of the pyrimidine nucleotides present in the double-stranded siNA molecule comprises a sugar modification, and wherein the nucleotide sequence of the antisense strand is complementary to a nucleotide sequence of the SARS RNA or a portion thereof that is present in the SARS RNA.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention in a pharmaceutically acceptable carrier or diluent.

In a non-limiting example, the introduction of chemically-modified nucleotides into nucleic acid molecules provides a powerful tool in overcoming potential limitations of *in vivo* stability and bioavailability inherent to native RNA molecules that are delivered exogenously. For example, the use of chemically-modified nucleic acid molecules can enable a lower dose of a particular nucleic acid molecule for a given therapeutic effect since chemically-modified nucleic acid molecules tend to have a longer half-life in serum. Furthermore, certain chemical modifications can improve the bioavailability of nucleic acid molecules by targeting particular cells or tissues and/or improving cellular uptake of the nucleic acid molecule. Therefore, even if the activity of

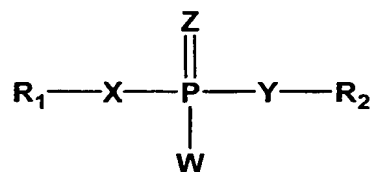
a chemically-modified nucleic acid molecule is reduced as compared to a native nucleic acid molecule, for example, when compared to an all-RNA nucleic acid molecule, the overall activity of the modified nucleic acid molecule can be greater than that of the native molecule due to improved stability and/or delivery of the molecule. Unlike native
5 unmodified siNA, chemically-modified siNA can also minimize the possibility of activating interferon activity in humans.

In any of the embodiments of siNA molecules described herein, the antisense region of a siNA molecule of the invention can comprise a phosphorothioate internucleotide linkage at the 3'-end of said antisense region. In any of the embodiments
10 of siNA molecules described herein, the antisense region can comprise about one to about five phosphorothioate internucleotide linkages at the 5'-end of said antisense region. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs of a siNA molecule of the invention can comprise ribonucleotides or deoxyribonucleotides that are chemically-modified at a nucleic acid sugar, base, or
15 backbone. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more universal base ribonucleotides. In any of the embodiments of siNA molecules described herein, the 3'-terminal nucleotide overhangs can comprise one or more acyclic nucleotides.

One embodiment of the invention provides an expression vector comprising a
20 nucleic acid sequence encoding at least one siNA molecule of the invention in a manner that allows expression of the nucleic acid molecule. Another embodiment of the invention provides a mammalian cell comprising such an expression vector. The mammalian cell can be a human cell. The siNA molecule of the expression vector can comprise a sense region and an antisense region. The antisense region can comprise
25 sequence complementary to a RNA or DNA sequence encoding SARS and the sense region can comprise sequence complementary to the antisense region. The siNA molecule can comprise two distinct strands having complementary sense and antisense regions. The siNA molecule can comprise a single strand having complementary sense and antisense regions.

In one embodiment, the nucleotide sequence of the antisense strand or a portion thereof of a siNA molecule of the invention is complementary to the nucleotide sequence of a SARS RNA or a portion thereof that is present in the RNA of all SARS isolates.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides comprising a backbone modified internucleotide linkage having Formula I:

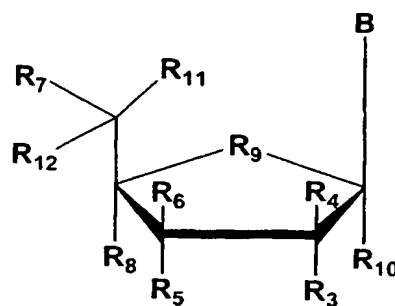


wherein each R1 and R2 is independently any nucleotide, non-nucleotide, or polynucleotide which can be naturally-occurring or chemically-modified, each X and Y is independently O, S, N, alkyl, or substituted alkyl, each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, or acetyl and wherein W, X, Y, and Z are optionally not all O. In another embodiment, a backbone modification of the invention comprises a phosphonoacetate and/or thiophosphonoacetate internucleotide linkage (see for example Sheehan et al., 2003, *Nucleic Acids Research*, 31, 4109-4118).

The chemically-modified internucleotide linkages having Formula I, for example, wherein any Z, W, X, and/or Y independently comprises a sulphur atom, can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) chemically-modified internucleotide linkages having Formula I at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified internucleotide linkages having Formula I at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine

nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine nucleotides with chemically-modified internucleotide linkages having Formula I in the sense strand, the antisense strand, or both strands. In another embodiment, a siNA molecule of the invention having internucleotide linkage(s) of Formula I also comprises a chemically-modified nucleotide or non-nucleotide having any of Formulae I-VII.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula II:

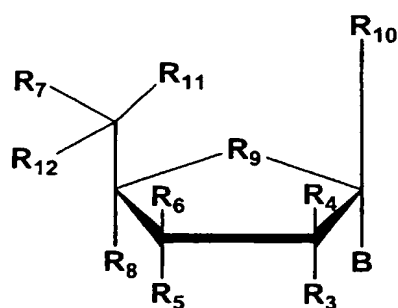


wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF₃, OCF₃, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO₂, NO₂, N₃, NH₂, aminoalkyl, aminoacid, aminoacyl, ONH₂, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH₂, S=O, CHF, or CF₂, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine,

pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula II can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotide or non-nucleotide of Formula II at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotides or non-nucleotides of Formula II at the 3'-end of the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) nucleotides or non-nucleotides having Formula III:



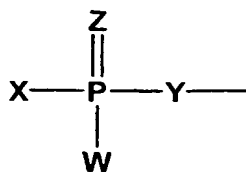
wherein each R3, R4, R5, R6, R7, R8, R10, R11 and R12 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-

aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R₉ is O, S, CH₂, S=O, CHF, or CF₂, and B is a nucleosidic base such as adenine, guanine, uracil, cytosine, thymine, 2-aminoadenosine, 5-methylcytosine, 2,6-diaminopurine, or any other non-naturally occurring base that can be employed to be complementary or non-complementary to target RNA or a non-nucleosidic base such as phenyl, naphthyl, 3-nitropyrrole, 5-nitroindole, nebularine, pyridone, pyridinone, or any other non-naturally occurring universal base that can be complementary or non-complementary to target RNA.

The chemically-modified nucleotide or non-nucleotide of Formula III can be present in one or both oligonucleotide strands of the siNA duplex, for example, in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide(s) or non-nucleotide(s) of Formula III at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) chemically-modified nucleotide or non-nucleotide of Formula III at the 3'-end of the sense strand, the antisense strand, or both strands.

In another embodiment, a siNA molecule of the invention comprises a nucleotide having Formula II or III, wherein the nucleotide having Formula II or III is in an inverted configuration. For example, the nucleotide having Formula II or III is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a 5'-terminal phosphate group having Formula IV:



wherein each X and Y is independently O, S, N, alkyl, substituted alkyl, or alkylhalo; wherein each Z and W is independently O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, aralkyl, alkylhalo, or acetyl; and wherein W, X, Y and Z are not all O.

- 5 In one embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary strand, for example, a strand complementary to a target RNA, wherein the siNA molecule comprises an all RNA siNA molecule. In another embodiment, the invention features a siNA molecule having a 5'-terminal phosphate group having Formula IV on the target-complementary
- 10 strand wherein the siNA molecule also comprises about 1 to about 3 (*e.g.*, about 1, 2, or 3) nucleotide 3'-terminal nucleotide overhangs having about 1 to about 4 (*e.g.*, about 1, 2, 3, or 4) deoxyribonucleotides on the 3'-end of one or both strands. In another embodiment, a 5'-terminal phosphate group having Formula IV is present on the target-complementary strand of a siNA molecule of the invention, for example a siNA
- 15 molecule having chemical modifications having any of Formulae I-VII.

- In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises one or more phosphorothioate internucleotide linkages. For example, in a
- 20 non-limiting example, the invention features a chemically-modified short interfering nucleic acid (siNA) having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in one siNA strand. In yet another embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) individually having about 1, 2, 3, 4, 5, 6, 7, 8 or more phosphorothioate internucleotide linkages in both siNA
- 25 strands. The phosphorothioate internucleotide linkages can be present in one or both oligonucleotide strands of the siNA duplex, for example in the sense strand, the antisense strand, or both strands. The siNA molecules of the invention can comprise one or more phosphorothioate internucleotide linkages at the 3'-end, the 5'-end, or both of the 3'- and

5'-ends of the sense strand, the antisense strand, or both strands. For example, an exemplary siNA molecule of the invention can comprise about 1 to about 5 or more (*e.g.*, about 1, 2, 3, 4, 5, or more) consecutive phosphorothioate internucleotide linkages at the 5'-end of the sense strand, the antisense strand, or both strands. In another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) pyrimidine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands. In yet another non-limiting example, an exemplary siNA molecule of the invention can comprise one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) purine phosphorothioate internucleotide linkages in the sense strand, the antisense strand, or both strands.

In one embodiment, the invention features a siNA molecule, wherein the sense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the sense strand comprises about 1 to about 5, specifically about 1, 2, 3, 4, or 5 phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, or more) 2'-deoxy,

2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more, pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5 or more, for example about 1, 2, 3, 4, 5, or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a siNA molecule, wherein the antisense strand comprises one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more phosphorothioate internucleotide linkages, and/or about one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 10 or more, specifically about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without one or more, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more

phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3' and 5'-ends, being present in the same or different strand.

In another embodiment, the invention features a siNA molecule, wherein the antisense strand comprises about 1 to about 5 or more, specifically about 1, 2, 3, 4, 5 or
5 more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the sense strand; and wherein the antisense strand comprises about 1 to about 5 or
10 more, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, and/or one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more) universal base modified nucleotides, and optionally a terminal cap molecule at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of the antisense strand. In another
15 embodiment, one or more, for example about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more pyrimidine nucleotides of the sense and/or antisense siNA strand are chemically-modified with 2'-deoxy, 2'-O-methyl and/or 2'-deoxy-2'-fluoro nucleotides, with or without about 1 to about 5, for example about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages and/or a terminal cap molecule at the 3'-end, the 5'-end, or both
20 of the 3'- and 5'-ends, being present in the same or different strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule having about 1 to about 5, specifically about 1, 2, 3, 4, 5 or more phosphorothioate internucleotide linkages in each strand of the siNA molecule.

In another embodiment, the invention features a siNA molecule comprising 2'-5'
25 internucleotide linkages. The 2'-5' internucleotide linkage(s) can be at the 3'-end, the 5'-end, or both of the 3'- and 5'-ends of one or both siNA sequence strands. In addition, the 2'-5' internucleotide linkage(s) can be present at various other positions within one or both siNA sequence strands, for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more including every internucleotide linkage of a pyrimidine nucleotide in one or both strands
30 of the siNA molecule can comprise a 2'-5' internucleotide linkage, or about 1, 2, 3, 4, 5,

6, 7, 8, 9, 10, or more including every internucleotide linkage of a purine nucleotide in one or both strands of the siNA molecule can comprise a 2'-5' internucleotide linkage.

In another embodiment, a chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified, wherein each strand is about 18 to about 27 (*e.g.*, about 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27) nucleotides in length, wherein the duplex has about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the chemical modification comprises a structure having any of Formulae I-VII. For example, an exemplary chemically-modified siNA molecule of the invention comprises a duplex having two strands, one or both of which can be chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein each strand consists of about 21 nucleotides, each having a 2-nucleotide 3'-terminal nucleotide overhang, and wherein the duplex has about 19 base pairs. In another embodiment, a siNA molecule of the invention comprises a single stranded hairpin structure, wherein the siNA is about 36 to about 70 (*e.g.*, about 36, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 18 to about 23 (*e.g.*, about 18, 19, 20, 21, 22, or 23) base pairs, and wherein the siNA can include a chemical modification comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 42 to about 50 (*e.g.*, about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a chemical modification having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 19 base pairs and a 2-nucleotide 3'-terminal nucleotide overhang. In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. For example, a linear hairpin siNA molecule of the invention is designed such that degradation of the loop portion of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

In another embodiment, a siNA molecule of the invention comprises a hairpin structure, wherein the siNA is about 25 to about 50 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31,

32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 25 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms a hairpin structure having about 3 to about 23 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, a linear hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is biodegradable. In another embodiment, a linear hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

In another embodiment, a siNA molecule of the invention comprises an asymmetric hairpin structure, wherein the siNA is about 25 to about 50 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides in length having about 3 to about 20 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) base pairs, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a linear oligonucleotide having about 25 to about 35 (*e.g.*, about 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35) nucleotides that is chemically-modified with one or more chemical modifications having any of Formulae I-VII or any combination thereof, wherein the linear oligonucleotide forms an asymmetric hairpin structure having about 3 to about 18 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 or 18) base pairs and a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV). In another embodiment, an asymmetric hairpin siNA molecule of the invention contains a stem loop motif, wherein the loop portion of the siNA molecule is

biodegradable. In another embodiment, an asymmetric hairpin siNA molecule of the invention comprises a loop portion comprising a non-nucleotide linker.

In another embodiment, a siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising sense and antisense regions, wherein the antisense region is about 16 to about 25 (*e.g.*,
5 about 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25) nucleotides in length, wherein the sense region is about 3 to about 18 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides in length, wherein the sense region and the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more
10 chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises an asymmetric double stranded structure having separate polynucleotide strands comprising sense and antisense regions, wherein the antisense region is about 18 to about 22 (*e.g.*, about 18, 19, 20, 21, or 22) nucleotides in length and
15 wherein the sense region is about 3 to about 15 (*e.g.*, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15) nucleotides in length, wherein the sense region the antisense region have at least 3 complementary nucleotides, and wherein the siNA can include one or more chemical modifications comprising a structure having any of Formulae I-VII or any combination thereof. In another embodiment, the asymmetric double stranded siNA
20 molecule can also have a 5'-terminal phosphate group that can be chemically modified as described herein (for example a 5'-terminal phosphate group having Formula IV).

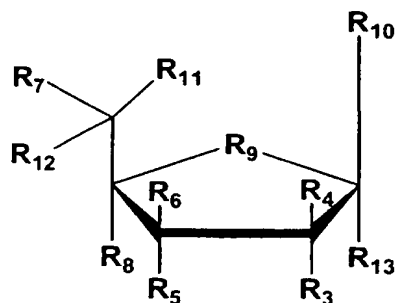
In another embodiment, a siNA molecule of the invention comprises a circular nucleic acid molecule, wherein the siNA is about 38 to about 70 (*e.g.*, about 38, 40, 45, 50, 55, 60, 65, or 70) nucleotides in length having about 18 to about 23 (*e.g.*, about 18,
25 19, 20, 21, 22, or 23) base pairs, and wherein the siNA can include a chemical modification, which comprises a structure having any of Formulae I-VII or any combination thereof. For example, an exemplary chemically-modified siNA molecule of the invention comprises a circular oligonucleotide having about 42 to about 50 (*e.g.*, about 42, 43, 44, 45, 46, 47, 48, 49, or 50) nucleotides that is chemically-modified with a
30 chemical modification having any of Formulae I-VII or any combination thereof,

wherein the circular oligonucleotide forms a dumbbell shaped structure having about 19 base pairs and 2 loops.

In another embodiment, a circular siNA molecule of the invention contains two loop motifs, wherein one or both loop portions of the siNA molecule is biodegradable.

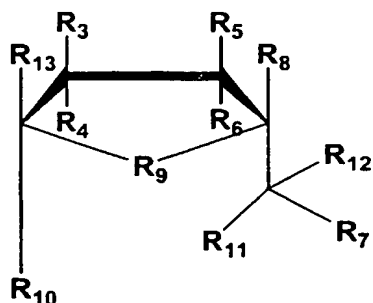
- 5 For example, a circular siNA molecule of the invention is designed such that degradation of the loop portions of the siNA molecule *in vivo* can generate a double-stranded siNA molecule with 3'-terminal overhangs, such as 3'-terminal nucleotide overhangs comprising about 2 nucleotides.

- 10 In one embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) abasic moiety, for example a compound having Formula V:



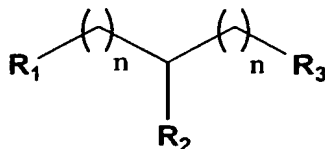
- 15 wherein each R3, R4, R5, R6, R7, R8, R10, R11, R12, and R13 is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF3, OCF3, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO2, NO2, N3, NH2, aminoalkyl, aminoacid, aminoacyl, ONH2, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R9 is O, S, CH2, S=O, CHF, or CF2.

- 20 In one embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) inverted abasic moiety, for example a compound having Formula VI:



wherein each R₃, R₄, R₅, R₆, R₇, R₈, R₁₀, R₁₁, R₁₂, and R₁₃ is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF₃, OCF₃, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO₂, NO₂, N₃, NH₂, aminoalkyl, aminoacid, aminoacyl, ONH₂, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or group having Formula I or II; R₉ is O, S, CH₂, S=O, CHF, or CF₂, and either R₂, R₃, R₈ or R₁₃ serve as points of attachment to the siNA molecule of the invention.

In another embodiment, a siNA molecule of the invention comprises at least one (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) substituted polyalkyl moieties, for example a compound having Formula VII:



wherein each *n* is independently an integer from 1 to 12, each R₁, R₂ and R₃ is independently H, OH, alkyl, substituted alkyl, alkaryl or aralkyl, F, Cl, Br, CN, CF₃, OCF₃, OCN, O-alkyl, S-alkyl, N-alkyl, O-alkenyl, S-alkenyl, N-alkenyl, SO-alkyl, alkyl-OSH, alkyl-OH, O-alkyl-OH, O-alkyl-SH, S-alkyl-OH, S-alkyl-SH, alkyl-S-alkyl, alkyl-O-alkyl, ONO₂, NO₂, N₃, NH₂, aminoalkyl, aminoacid, aminoacyl, ONH₂, O-aminoalkyl, O-aminoacid, O-aminoacyl, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, or a group having Formula I, and R₁, R₂ or R₃ serves as points of attachment to the siNA molecule of the invention.

In another embodiment, the invention features a compound having Formula VII, wherein R1 and R2 are hydroxyl (OH) groups, $n = 1$, and R3 comprises O and is the point of attachment to the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both strands of a double-stranded siNA molecule of the invention or to a single-stranded siNA molecule of the invention. This modification is referred to herein as "glyceryl" (for example modification 6 in **Figure 10**).

In another embodiment, a moiety having any of Formula V, VI or VII of the invention is at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of a siNA molecule of the invention. For example, a moiety having Formula V, VI or VII can be present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense strand, the sense strand, or both antisense and sense strands of the siNA molecule. In addition, a moiety having Formula VII can be present at the 3'-end or the 5'-end of a hairpin siNA molecule as described herein.

In another embodiment, a siNA molecule of the invention comprises an abasic residue having Formula V or VI, wherein the abasic residue having Formula VI or VI is connected to the siNA construct in a 3'-3', 3'-2', 2'-3', or 5'-5' configuration, such as at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of one or both siNA strands.

In one embodiment, a siNA molecule of the invention comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) locked nucleic acid (LNA) nucleotides, for example at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In another embodiment, a siNA molecule of the invention comprises one or more (*e.g.*, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) acyclic nucleotides, for example at the 5'-end, the 3'-end, both of the 5' and 3'-ends, or any combination thereof, of the siNA molecule.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-

2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality
5 of purine nucleotides are 2'-deoxy purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-
10 2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-deoxy purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), wherein any nucleotides
15 comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-
20 2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the sense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a
25 plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising a sense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-
30 2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), wherein any (*e.g.*, one or more or all) purine

nucleotides present in the sense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in said sense region are 2'-
5 deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are
10 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine
20 nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), wherein any (*e.g.*, one or more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (*e.g.*, wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and wherein any nucleotides comprising a 3'-terminal nucleotide overhang that are present in
25 said antisense region are 2'-deoxy nucleotides.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (*e.g.*, one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (*e.g.*, wherein all pyrimidine nucleotides are
30 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (*e.g.*, one or

more or all) purine nucleotides present in the antisense region are 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides).

5 In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention comprising an antisense region, wherein any (e.g., one or more or all) pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any (e.g., one or
10 more or all) purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides).

In one embodiment, the invention features a chemically-modified short interfering nucleic acid (siNA) molecule of the invention capable of mediating RNA interference
15 (RNAi) against SARS inside a cell or reconstituted *in vitro* system comprising a sense region, wherein one or more pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and one or more purine
20 nucleotides present in the sense region are 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides), and an antisense region, wherein one or more pyrimidine nucleotides present in the antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro
25 pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and one or more purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). The sense region and/or the antisense region can have a
30 terminal cap modification, such as any modification described herein or shown in **Figure 10**, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the

sense and/or antisense sequence. The sense and/or antisense region can optionally further comprise a 3'-terminal nucleotide overhang having about 1 to about 4 (e.g., about 1, 2, 3, or 4) 2'-deoxynucleotides. The overhang nucleotides can further comprise one or more (e.g., about 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages. Non-limiting examples of these chemically-modified siNAs are shown in **Figures 4 and 5** and **Tables III and IV** herein. In any of these described embodiments, the purine nucleotides present in the sense region are alternatively 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides) and one or more purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). Also, in any of these embodiments, one or more purine nucleotides present in the sense region are alternatively purine ribonucleotides (e.g., wherein all purine nucleotides are purine ribonucleotides or alternately a plurality of purine nucleotides are purine ribonucleotides) and any purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides). Additionally, in any of these embodiments, one or more purine nucleotides present in the sense region and/or present in the antisense region are alternatively selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides (e.g., wherein all purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides or alternately a plurality of purine nucleotides are selected from the group consisting of 2'-deoxy nucleotides, locked nucleic acid (LNA) nucleotides, 2'-methoxyethyl nucleotides, 4'-thionucleotides, and 2'-O-methyl nucleotides).

In another embodiment, any modified nucleotides present in the siNA molecules of the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, comprise modified nucleotides having properties or characteristics similar to naturally occurring

ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the siNA molecules of the invention, preferably in the antisense strand of the siNA molecules of the invention, but also optionally in the sense and/or both antisense and sense strands, are resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi. Non-limiting examples of nucleotides having a northern configuration include locked nucleic acid (LNA) nucleotides (e.g., 2'-O, 4'-C-methylene-(D-ribofuranosyl) nucleotides); 2'-methoxyethoxy (MOE) nucleotides; 2'-methyl-thio-ethyl, 2'-deoxy-2'-fluoro nucleotides, 2'-deoxy-2'-chloro nucleotides, 2'-azido nucleotides, and 2'-O-methyl nucleotides.

In one embodiment, the sense strand of a double stranded siNA molecule of the invention comprises a terminal cap moiety, (see for example **Figure 10**) such as an inverted deoxyabaisc moiety, at the 3'-end, 5'-end, or both 3' and 5'-ends of the sense strand.

In one embodiment, the invention features a chemically-modified short interfering nucleic acid molecule (siNA) capable of mediating RNA interference (RNAi) against SARS inside a cell or reconstituted *in vitro* system, wherein the chemical modification comprises a conjugate covalently attached to the chemically-modified siNA molecule. Non-limiting examples of conjugates contemplated by the invention include conjugates and ligands described in Vargeese *et al.*, USSN 10/427,160, filed April 30, 2003, incorporated by reference herein in its entirety, including the drawings. In another embodiment, the conjugate is covalently attached to the chemically-modified siNA molecule via a biodegradable linker. In one embodiment, the conjugate molecule is attached at the 3'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In another embodiment, the conjugate molecule is attached at the 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule. In yet another embodiment, the conjugate molecule is attached both the 3'-end and 5'-end of either the sense strand, the antisense strand, or both strands of the chemically-modified siNA molecule, or any

combination thereof. In one embodiment, a conjugate molecule of the invention comprises a molecule that facilitates delivery of a chemically-modified siNA molecule into a biological system, such as a cell. In another embodiment, the conjugate molecule attached to the chemically-modified siNA molecule is a polyethylene glycol, human
5 serum albumin, or a ligand for a cellular receptor that can mediate cellular uptake. Examples of specific conjugate molecules contemplated by the instant invention that can be attached to chemically-modified siNA molecules are described in Vargeese *et al.*, U.S. Serial No. 10/201,394, filed July 22, 2002, incorporated by reference herein. The type of conjugates used and the extent of conjugation of siNA molecules of the invention
10 can be evaluated for improved pharmacokinetic profiles, bioavailability, and/or stability of siNA constructs while at the same time maintaining the ability of the siNA to mediate RNAi activity. As such, one skilled in the art can screen siNA constructs that are modified with various conjugates to determine whether the siNA conjugate complex possesses improved properties while maintaining the ability to mediate RNAi, for
15 example in animal models as are generally known in the art.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule of the invention, wherein the siNA further comprises a nucleotide, non-nucleotide, or mixed nucleotide/non-nucleotide linker that joins the sense region of the siNA to the antisense region of the siNA. In one embodiment, a nucleotide linker of the
20 invention can be a linker of ≥ 2 nucleotides in length, for example about 3, 4, 5, 6, 7, 8, 9, or 10 nucleotides in length. In another embodiment, the nucleotide linker can be a nucleic acid aptamer. By "aptamer" or "nucleic acid aptamer" as used herein is meant a nucleic acid molecule that binds specifically to a target molecule wherein the nucleic acid molecule has sequence that comprises a sequence recognized by the target molecule
25 in its natural setting. Alternately, an aptamer can be a nucleic acid molecule that binds to a target molecule where the target molecule does not naturally bind to a nucleic acid. The target molecule can be any molecule of interest. For example, the aptamer can be used to bind to a ligand-binding domain of a protein, thereby preventing interaction of the naturally occurring ligand with the protein. This is a non-limiting example and those
30 in the art will recognize that other embodiments can be readily generated using techniques generally known in the art. (See, for example, Gold *et al.*, 1995, *Annu. Rev. Biochem.*, 64, 763; Brody and Gold, 2000, *J. Biotechnol.*, 74, 5; Sun, 2000, *Curr. Opin.*

Mol. Ther., 2, 100; Kusser, 2000, *J. Biotechnol.*, 74, 27; Hermann and Patel, 2000, *Science*, 287, 820; and Jayasena, 1999, *Clinical Chemistry*, 45, 1628.)

In yet another embodiment, a non-nucleotide linker of the invention comprises abasic nucleotide, polyether, polyamine, polyamide, peptide, carbohydrate, lipid, polyhydrocarbon, or other polymeric compounds (e.g. polyethylene glycols such as those having between 2 and 100 ethylene glycol units). Specific examples include those described by Seela and Kaiser, *Nucleic Acids Res.* 1990, 18:6353 and *Nucleic Acids Res.* 1987, 15:3113; Cload and Schepartz, *J. Am. Chem. Soc.* 1991, 113:6324; Richardson and Schepartz, *J. Am. Chem. Soc.* 1991, 113:5109; Ma *et al.*, *Nucleic Acids Res.* 1993, 21:2585 and *Biochemistry* 1993, 32:1751; Durand *et al.*, *Nucleic Acids Res.* 1990, 18:6353; McCurdy *et al.*, *Nucleosides & Nucleotides* 1991, 10:287; Jsche *et al.*, *Tetrahedron Lett.* 1993, 34:301; Ono *et al.*, *Biochemistry* 1991, 30:9914; Arnold *et al.*, International Publication No. WO 89/02439; Usman *et al.*, International Publication No. WO 95/06731; Dudycz *et al.*, International Publication No. WO 95/11910 and Ferentz and Verdine, *J. Am. Chem. Soc.* 1991, 113:4000, all hereby incorporated by reference herein. A "non-nucleotide" further means any group or compound that can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound can be abasic in that it does not contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine, for example at the C1 position of the sugar.

In one embodiment, the invention features a short interfering nucleic acid (siNA) molecule capable of mediating RNA interference (RNAi) inside a cell or reconstituted *in vitro* system, wherein one or both strands of the siNA molecule that are assembled from two separate oligonucleotides do not comprise any ribonucleotides. For example, a siNA molecule can be assembled from a single oligonucleotide where the sense and antisense regions of the siNA comprise separate oligonucleotides not having any ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotides. In another example, a siNA molecule can be assembled from a single oligonucleotide where the sense and antisense regions of the siNA are linked or circularized by a nucleotide or non-nucleotide linker as described herein, wherein the oligonucleotide does not have any

ribonucleotides (e.g., nucleotides having a 2'-OH group) present in the oligonucleotide. Applicant has surprisingly found that the presence of ribonucleotides (e.g., nucleotides having a 2'-hydroxyl group) within the siNA molecule is not required or essential to support RNAi activity. As such, in one embodiment, all positions within the siNA can include chemically modified nucleotides and/or non-nucleotides such as nucleotides and or non-nucleotides having Formula I, II, III, IV, V, VI, or VII or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA molecule that mediates RNAi activity in a cell or reconstituted in vitro system comprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group. In another embodiment, the single stranded siNA molecule of the invention comprises a 5'-terminal phosphate group and a 3'-terminal phosphate group (e.g., a 2',3'-cyclic phosphate). In another embodiment, the single stranded siNA molecule of the invention comprises about 19 to about 29 (e.g., about 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29) nucleotides. In yet another embodiment, the single stranded siNA molecule of the invention comprises one or more chemically modified nucleotides or non-nucleotides described herein. For example, all the positions within the siNA molecule can include chemically-modified nucleotides such as nucleotides having any of Formulae I-VII, or any combination thereof to the extent that the ability of the siNA molecule to support RNAi activity in a cell is maintained.

In one embodiment, a siNA molecule of the invention is a single stranded siNA molecule that mediates RNAi activity in a cell or reconstituted in vitro system comprising a single stranded polynucleotide having complementarity to a target nucleic acid sequence, wherein one or more pyrimidine nucleotides present in the siNA are 2'-deoxy-2'-fluoro pyrimidine nucleotides (e.g., wherein all pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides or alternately a plurality of pyrimidine nucleotides are 2'-deoxy-2'-fluoro pyrimidine nucleotides), and wherein any purine nucleotides present in the antisense region are 2'-O-methyl purine nucleotides (e.g., wherein all purine

nucleotides are 2'-O-methyl purine nucleotides or alternately a plurality of purine nucleotides are 2'-O-methyl purine nucleotides), and a terminal cap modification, such as any modification described herein or shown in **Figure 10**, that is optionally present at the 3'-end, the 5'-end, or both of the 3' and 5'-ends of the antisense sequence. The siNA
5 optionally further comprises about 1 to about 4 or more (e.g., about 1, 2, 3, 4 or more) terminal 2'-deoxynucleotides at the 3'-end of the siNA molecule, wherein the terminal nucleotides can further comprise one or more (e.g., 1, 2, 3, 4 or more) phosphorothioate, phosphonoacetate, and/or thiophosphonoacetate internucleotide linkages, and wherein the siNA optionally further comprises a terminal phosphate group, such as a 5'-terminal
10 phosphate group. In any of these embodiments, any purine nucleotides present in the antisense region are alternatively 2'-deoxy purine nucleotides (e.g., wherein all purine nucleotides are 2'-deoxy purine nucleotides or alternately a plurality of purine nucleotides are 2'-deoxy purine nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA (i.e., purine nucleotides present in the sense
15 and/or antisense region) can alternatively be locked nucleic acid (LNA) nucleotides (e.g., wherein all purine nucleotides are LNA nucleotides or alternately a plurality of purine nucleotides are LNA nucleotides). Also, in any of these embodiments, any purine nucleotides present in the siNA are alternatively 2'-methoxyethyl purine nucleotides (e.g., wherein all purine nucleotides are 2'-methoxyethyl purine nucleotides or
20 alternately a plurality of purine nucleotides are 2'-methoxyethyl purine nucleotides). In another embodiment, any modified nucleotides present in the single stranded siNA molecules of the invention comprise modified nucleotides having properties or characteristics similar to naturally occurring ribonucleotides. For example, the invention features siNA molecules including modified nucleotides having a Northern conformation
25 (e.g., Northern pseudorotation cycle, see for example Saenger, *Principles of Nucleic Acid Structure*, Springer-Verlag ed., 1984). As such, chemically modified nucleotides present in the single stranded siNA molecules of the invention are preferably resistant to nuclease degradation while at the same time maintaining the capacity to mediate RNAi.

In one embodiment, the invention features a method for modulating the expression
30 of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the

siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

5 In one embodiment, the invention features a method for modulating the expression of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequence of the target RNA; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

10 In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

15 In another embodiment, the invention features a method for modulating the expression of two or more SARS genes within a cell comprising: (a) synthesizing one or more siNA molecules of the invention, which can be chemically-modified, wherein the siNA strands comprise sequences complementary to RNA of the SARS genes and wherein the sense strand sequences of the siNAs comprise sequences identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA molecules into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

20 In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the sequences of the target RNAs; and (b) introducing the siNA

molecule into a cell under conditions suitable to modulate the expression of the SARS genes in the cell.

In one embodiment, siNA molecules of the invention are used as reagents in *ex vivo* applications. For example, siNA reagents are introduced into tissue or cells that are
5 transplanted into a subject for therapeutic effect. The cells and/or tissue can be derived from an organism or subject that later receives the explant, or can be derived from another organism or subject prior to transplantation. The siNA molecules can be used to modulate the expression of one or more genes in the cells or tissue, such that the cells or tissue obtain a desired phenotype or are able to perform a function when transplanted in
10 *vivo*. In one embodiment, certain target cells from a patient are extracted. These extracted cells are contacted with siNAs targeting a specific nucleotide sequence within the cells under conditions suitable for uptake of the siNAs by these cells (e.g. using delivery reagents such as cationic lipids, liposomes and the like or using techniques such as electroporation to facilitate the delivery of siNAs into cells). The cells are then
15 reintroduced back into the same patient or other patients. In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the siNA molecule into a
20 cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that organism.

25 In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene and wherein the sense strand sequence of the siNA comprises a sequence identical or substantially similar to the
30 sequence of the target RNA; and (b) introducing the siNA molecule into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate

the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that organism.

5 In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular
10 organism under conditions suitable to modulate the expression of the SARS genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS genes in that organism.

15 In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands comprises a sequence complementary to RNA of the SARS gene; and (b) introducing the siNA molecule into the organism under conditions suitable to modulate the expression of
20 the SARS gene in the organism. The level of SARS protein or RNA can be determined as is known in the art.

 In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein one of the
25 siNA strands comprises a sequence complementary to RNA of the SARS genes; and (b) introducing the siNA molecules into the organism under conditions suitable to modulate the expression of the SARS genes in the organism. The level of SARS protein or RNA can be determined as is known in the art.

 In one embodiment, the invention features a method for modulating the expression
30 of a SARS gene within a cell comprising: (a) synthesizing a siNA molecule of the

invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecule into a cell under conditions suitable to modulate the expression of the SARS gene in the cell.

5 In another embodiment, the invention features a method for modulating the expression of more than one SARS gene within a cell comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) contacting the cell in vitro or in vivo with the siNA molecule under
10 conditions suitable to modulate the expression of the SARS genes in the cell.

 In one embodiment, the invention features a method of modulating the expression of a SARS gene in a tissue explant comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b)
15 contacting the cell of the tissue explant derived from a particular organism with the siNA molecule under conditions suitable to modulate the expression of the SARS gene in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS gene in that
20 organism.

 In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in a tissue explant comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS
25 gene; and (b) introducing the siNA molecules into a cell of the tissue explant derived from a particular organism under conditions suitable to modulate the expression of the SARS genes in the tissue explant. In another embodiment, the method further comprises introducing the tissue explant back into the organism the tissue was derived from or into another organism under conditions suitable to modulate the expression of the SARS
30 genes in that organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecule into the organism under conditions suitable to modulate the expression of the SARS gene in the organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising: (a) synthesizing siNA molecules of the invention, which can be chemically-modified, wherein the siNA comprises a single stranded sequence having complementarity to RNA of the SARS gene; and (b) introducing the siNA molecules into the organism under conditions suitable to modulate the expression of the SARS genes in the organism.

In one embodiment, the invention features a method of modulating the expression of a SARS gene in an organism comprising contacting the organism with a siNA molecule of the invention under conditions suitable to modulate the expression of the SARS gene in the organism.

In another embodiment, the invention features a method of modulating the expression of more than one SARS gene in an organism comprising contacting the organism with one or more siNA molecules of the invention under conditions suitable to modulate the expression of the SARS genes in the organism.

The siNA molecules of the invention can be designed to down regulate or inhibit target (e.g., SARS) gene expression through RNAi targeting of a variety of RNA molecules. In one embodiment, the siNA molecules of the invention are used to target various RNAs corresponding to a target gene. Non-limiting examples of such RNAs include messenger RNA (mRNA), alternate RNA splice variants of target gene(s), post-transcriptionally modified RNA of target gene(s), pre-mRNA of target gene(s), and/or RNA templates. If alternate splicing produces a family of transcripts that are distinguished by usage of appropriate exons, the instant invention can be used to inhibit gene expression through the appropriate exons to specifically inhibit or to distinguish among the functions of gene family members. For example, a protein that contains an

alternatively spliced transmembrane domain can be expressed in both membrane bound and secreted forms. Use of the invention to target the exon containing the transmembrane domain can be used to determine the functional consequences of pharmaceutical targeting of membrane bound as opposed to the secreted form of the protein. Non-limiting examples of applications of the invention relating to targeting these RNA molecules include therapeutic pharmaceutical applications, pharmaceutical discovery applications, molecular diagnostic and gene function applications, and gene mapping, for example using single nucleotide polymorphism mapping with siNA molecules of the invention. Such applications can be implemented using known gene sequences or from partial sequences available from an expressed sequence tag (EST).

In another embodiment, the siNA molecules of the invention are used to target conserved sequences corresponding to a gene family or gene families such as SARS family genes. As such, siNA molecules targeting multiple SARS targets can provide increased therapeutic effect. In addition, siNA can be used to characterize pathways of gene function in a variety of applications. For example, the present invention can be used to inhibit the activity of target gene(s) in a pathway to determine the function of uncharacterized gene(s) in gene function analysis, mRNA function analysis, or translational analysis. The invention can be used to determine potential target gene pathways involved in various diseases and conditions toward pharmaceutical development. The invention can be used to understand pathways of gene expression involved in, for example, the progression and/or maintenance of SARS virus infection, acute respiratory failure, viral pneumonia, and other indications that can respond to the level of SARS in a cell or tissue.

In one embodiment, siNA molecule(s) and/or methods of the invention are used to down regulate the expression of gene(s) that encode RNA referred to by Genbank Accession, for example SARS genes encoding RNA sequence(s) referred to herein by Genbank Accession number, for example, Genbank Accession Nos. shown in **Table I**.

In one embodiment, the invention features a method comprising: (a) generating a library of siNA constructs having a predetermined complexity; and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target RNA sequence. In one embodiment, the siNA molecules of (a) have strands of

a fixed length, for example, about 23 nucleotides in length. In another embodiment, the siNA molecules of (a) are of differing length, for example having strands of about 19 to about 25 (e.g., about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described
5 herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNase protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the
10 art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

In one embodiment, the invention features a method comprising: (a) generating a randomized library of siNA constructs having a predetermined complexity, such as of 4^N , where N represents the number of base paired nucleotides in each of the siNA construct
15 strands (eg. for a siNA construct having 21 nucleotide sense and antisense strands with 19 base pairs, the complexity would be 4^{19}); and (b) assaying the siNA constructs of (a) above, under conditions suitable to determine RNAi target sites within the target SARS RNA sequence. In another embodiment, the siNA molecules of (a) have strands of a fixed length, for example about 23 nucleotides in length. In yet another embodiment, the
20 siNA molecules of (a) are of differing length, for example having strands of about 19 to about 25 (e.g., about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described in Example 7 herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. In another embodiment, fragments of SARS RNA are
25 analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNase protection assays, to determine the most suitable target site(s) within the target SARS RNA sequence. The target SARS RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by cellular expression in *in vivo* systems.

30 In another embodiment, the invention features a method comprising: (a) analyzing the sequence of a RNA target encoded by a target gene; (b) synthesizing one or more sets

of siNA molecules having sequence complementary to one or more regions of the RNA of (a); and (c) assaying the siNA molecules of (b) under conditions suitable to determine RNAi targets within the target RNA sequence. In one embodiment, the siNA molecules of (b) have strands of a fixed length, for example about 23 nucleotides in length. In another embodiment, the siNA molecules of (b) are of differing length, for example having strands of about 19 to about 25 (e.g., about 19, 20, 21, 22, 23, 24, or 25) nucleotides in length. In one embodiment, the assay can comprise a reconstituted *in vitro* siNA assay as described herein. In another embodiment, the assay can comprise a cell culture system in which target RNA is expressed. Fragments of target RNA are analyzed for detectable levels of cleavage, for example by gel electrophoresis, northern blot analysis, or RNase protection assays, to determine the most suitable target site(s) within the target RNA sequence. The target RNA sequence can be obtained as is known in the art, for example, by cloning and/or transcription for *in vitro* systems, and by expression in *in vivo* systems.

By "target site" is meant a sequence within a target RNA that is "targeted" for cleavage mediated by a siNA construct which contains sequences within its antisense region that are complementary to the target sequence.

By "detectable level of cleavage" is meant cleavage of target RNA (and formation of cleaved product RNAs) to an extent sufficient to discern cleavage products above the background of RNAs produced by random degradation of the target RNA. Production of cleavage products from 1-5% of the target RNA is sufficient to detect above the background for most methods of detection.

In one embodiment, the invention features a composition comprising a siNA molecule of the invention, which can be chemically-modified, in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a pharmaceutical composition comprising siNA molecules of the invention, which can be chemically-modified, targeting one or more genes in a pharmaceutically acceptable carrier or diluent. In another embodiment, the invention features a method for diagnosing a disease or condition in a subject comprising administering to the subject a composition of the invention under conditions suitable for the diagnosis of the disease or condition in the subject. In another embodiment, the invention features a method for

treating or preventing a disease or condition in a subject, comprising administering to the subject a composition of the invention under conditions suitable for the treatment or prevention of the disease or condition in the subject, alone or in conjunction with one or more other therapeutic compounds. In yet another embodiment, the invention features a method for reducing or preventing tissue rejection in a subject comprising administering to the subject a composition of the invention under conditions suitable for the reduction or prevention of tissue rejection in the subject.

In another embodiment, the invention features a method for validating a SARS gene target, comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a SARS target gene; (b) introducing the siNA molecule into a cell, tissue, or organism under conditions suitable for modulating expression of the SARS target gene in the cell, tissue, or organism; and (c) determining the function of the gene by assaying for any phenotypic change in the cell, tissue, or organism.

In another embodiment, the invention features a method for validating a SARS target comprising: (a) synthesizing a siNA molecule of the invention, which can be chemically-modified, wherein one of the siNA strands includes a sequence complementary to RNA of a SARS target gene; (b) introducing the siNA molecule into a biological system under conditions suitable for modulating expression of the SARS target gene in the biological system; and (c) determining the function of the gene by assaying for any phenotypic change in the biological system.

By "biological system" is meant, material, in a purified or unpurified form, from biological sources, including but not limited to human or animal, wherein the system comprises the components required for RNAi activity. The term "biological system" includes, for example, a cell, tissue, or organism, or extract thereof. The term biological system also includes reconstituted RNAi systems that can be used in an *in vitro* setting.

By "phenotypic change" is meant any detectable change to a cell that occurs in response to contact or treatment with a nucleic acid molecule of the invention (e.g., siNA). Such detectable changes include, but are not limited to, changes in shape, size, proliferation, motility, protein expression or RNA expression or other physical or

chemical changes as can be assayed by methods known in the art. The detectable change can also include expression of reporter genes/molecules such as Green Florescent Protein (GFP) or various tags that are used to identify an expressed protein or any other cellular component that can be assayed.

5 In one embodiment, the invention features a kit containing a siNA molecule of the invention, which can be chemically-modified, that can be used to modulate the expression of a SARS target gene in a biological system, including, for example, in a cell, tissue, or organism. In another embodiment, the invention features a kit containing more than one siNA molecule of the invention, which can be chemically-modified, that
10 can be used to modulate the expression of more than one SARS target gene in a biological system, including, for example, in a cell, tissue, or organism.

In one embodiment, the invention features a cell containing one or more siNA molecules of the invention, which can be chemically-modified. In another embodiment, the cell containing a siNA molecule of the invention is a mammalian cell. In yet another
15 embodiment, the cell containing a siNA molecule of the invention is a human cell.

In one embodiment, the synthesis of a siNA molecule of the invention, which can be chemically-modified, comprises: (a) synthesis of two complementary strands of the siNA molecule; (b) annealing the two complementary strands together under conditions suitable to obtain a double-stranded siNA molecule. In another embodiment, synthesis
20 of the two complementary strands of the siNA molecule is by solid phase oligonucleotide synthesis. In yet another embodiment, synthesis of the two complementary strands of the siNA molecule is by solid phase tandem oligonucleotide synthesis.

In one embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing a first oligonucleotide sequence strand of
25 the siNA molecule, wherein the first oligonucleotide sequence strand comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of the second oligonucleotide sequence strand of the siNA; (b) synthesizing the second oligonucleotide sequence strand of siNA on the scaffold of the first oligonucleotide sequence strand, wherein the second oligonucleotide sequence strand further comprises a chemical moiety
30 than can be used to purify the siNA duplex; (c) cleaving the linker molecule of (a) under

conditions suitable for the two siNA oligonucleotide strands to hybridize and form a stable duplex; and (d) purifying the siNA duplex utilizing the chemical moiety of the second oligonucleotide sequence strand. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example under hydrolysis conditions using an alkylamine base such as methylamine. In one embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place concomitantly. In another embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group, which can be employed in a trityl-on synthesis strategy as described herein. In yet another embodiment, the chemical moiety, such as a dimethoxytrityl group, is removed during purification, for example, using acidic conditions.

In a further embodiment, the method for siNA synthesis is a solution phase synthesis or hybrid phase synthesis wherein both strands of the siNA duplex are synthesized in tandem using a cleavable linker attached to the first sequence which acts as a scaffold for synthesis of the second sequence. Cleavage of the linker under conditions suitable for hybridization of the separate siNA sequence strands results in formation of the double-stranded siNA molecule.

In another embodiment, the invention features a method for synthesizing a siNA duplex molecule comprising: (a) synthesizing one oligonucleotide sequence strand of the siNA molecule, wherein the sequence comprises a cleavable linker molecule that can be used as a scaffold for the synthesis of another oligonucleotide sequence; (b) synthesizing a second oligonucleotide sequence having complementarity to the first sequence strand on the scaffold of (a), wherein the second sequence comprises the other strand of the double-stranded siNA molecule and wherein the second sequence further comprises a chemical moiety than can be used to isolate the attached oligonucleotide

sequence; (c) purifying the product of (b) utilizing the chemical moiety of the second oligonucleotide sequence strand under conditions suitable for isolating the full-length sequence comprising both siNA oligonucleotide strands connected by the cleavable linker and under conditions suitable for the two siNA oligonucleotide strands to
5 hybridize and form a stable duplex. In one embodiment, cleavage of the linker molecule in (c) above takes place during deprotection of the oligonucleotide, for example under hydrolysis conditions. In another embodiment, cleavage of the linker molecule in (c) above takes place after deprotection of the oligonucleotide. In another embodiment, the method of synthesis comprises solid phase synthesis on a solid support such as controlled
10 pore glass (CPG) or polystyrene, wherein the first sequence of (a) is synthesized on a cleavable linker, such as a succinyl linker, using the solid support as a scaffold. The cleavable linker in (a) used as a scaffold for synthesizing the second strand can comprise similar reactivity or differing reactivity as the solid support derivatized linker, such that cleavage of the solid support derivatized linker and the cleavable linker of (a) takes place
15 either concomitantly or sequentially. In one embodiment, the chemical moiety of (b) that can be used to isolate the attached oligonucleotide sequence comprises a trityl group, for example a dimethoxytrityl group.

In another embodiment, the invention features a method for making a double-stranded siNA molecule in a single synthetic process comprising: (a) synthesizing an
20 oligonucleotide having a first and a second sequence, wherein the first sequence is complementary to the second sequence, and the first oligonucleotide sequence is linked to the second sequence via a cleavable linker, and wherein a terminal 5'-protecting group, for example, a 5'-O-dimethoxytrityl group (5'-O-DMT) remains on the oligonucleotide having the second sequence; (b) deprotecting the oligonucleotide whereby the
25 deprotection results in the cleavage of the linker joining the two oligonucleotide sequences; and (c) purifying the product of (b) under conditions suitable for isolating the double-stranded siNA molecule, for example using a trityl-on synthesis strategy as described herein.

In another embodiment, the method of synthesis of siNA molecules of the
30 invention comprises the teachings of Scaringe *et al.*, US Patent Nos. 5,889,136; 6,008,400; and 6,111,086, incorporated by reference herein in their entirety.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications, for example, one or more chemical modifications having any of Formulae I-VII or any combination thereof that increases the nuclease resistance of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules with increased nuclease resistance comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased nuclease resistance.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the sense and antisense strands of the siNA construct.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the sense and antisense strands of the siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the sense and antisense strands of the siNA molecule.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target RNA sequence within a cell.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the binding affinity between the antisense strand of the siNA construct and a complementary target DNA sequence within a cell.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target RNA sequence.

In another embodiment, the invention features a method for generating siNA molecules with increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having increased binding affinity between the antisense strand of the siNA molecule and a complementary target DNA sequence.

In one embodiment, the invention features siNA constructs that mediate RNAi against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulate the polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA construct.

In another embodiment, the invention features a method for generating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to a chemically-modified siNA molecule comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules capable of mediating increased polymerase activity of a cellular polymerase capable of generating additional endogenous siNA molecules having sequence homology to the chemically-modified siNA molecule.

In one embodiment, the invention features chemically-modified siNA constructs that mediate RNAi against SARS in a cell, wherein the chemical modifications do not

significantly effect the interaction of siNA with a target RNA molecule, DNA molecule and/or proteins or other factors that are essential for RNAi in a manner that would decrease the efficacy of RNAi mediated by such siNA constructs.

In another embodiment, the invention features a method for generating siNA
5 molecules with improved RNAi activity against SARS comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity.

In yet another embodiment, the invention features a method for generating siNA
10 molecules with improved RNAi activity against SARS target RNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target RNA.

In yet another embodiment, the invention features a method for generating siNA
15 molecules with improved RNAi activity against SARS target DNA comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved RNAi activity against the target DNA.

In one embodiment, the invention features siNA constructs that mediate RNAi
20 against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that modulates the cellular uptake of the siNA construct.

In another embodiment, the invention features a method for generating siNA
molecules against SARS with improved cellular uptake comprising (a) introducing nucleotides having any of Formula I-VII or any combination thereof into a siNA
25 molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved cellular uptake.

In one embodiment, the invention features siNA constructs that mediate RNAi
against SARS, wherein the siNA construct comprises one or more chemical modifications described herein that increases the bioavailability of the siNA construct,

for example, by attaching polymeric conjugates such as polyethyleneglycol or equivalent conjugates that improve the pharmacokinetics of the siNA construct, or by attaching conjugates that target specific tissue types or cell types *in vivo*. Non-limiting examples of such conjugates are described in Vargeese *et al.*, U.S. Serial No. 10/201,394
5 incorporated by reference herein.

In one embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability, comprising (a) introducing a conjugate into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved
10 bioavailability. Such conjugates can include ligands for cellular receptors, such as peptides derived from naturally occurring protein ligands; protein localization sequences, including cellular ZIP code sequences; antibodies; nucleic acid aptamers; vitamins and other co-factors, such as folate and N-acetylgalactosamine; polymers, such as polyethyleneglycol (PEG); phospholipids; cholesterol; polyamines, such as spermine or
15 spermidine; and others.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is chemically
20 modified in a manner that it can no longer act as a guide sequence for efficiently mediating RNA interference and/or be recognized by cellular proteins that facilitate RNAi.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having
25 complementarity to said first sequence, wherein the second sequence is designed or modified in a manner that prevents its entry into the RNAi pathway as a guide sequence or as a sequence that is complementary to a target nucleic acid (e.g., RNA) sequence. Such design or modifications are expected to enhance the activity of siNA and/or
30 improve the specificity of siNA molecules of the invention. These modifications are also expected to minimize any off-target effects and/or associated toxicity.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence is incapable of
5 acting as a guide sequence for mediating RNA interference.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence does not have a
10 terminal 5'-hydroxyl (5'-OH) or 5'-phosphate group.

In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a
15 terminal cap moiety at the 5'-end of said second sequence. In one embodiment, the terminal cap moiety comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in **Figure 10**, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

20 In one embodiment, the invention features a double stranded short interfering nucleic acid (siNA) molecule that comprises a first nucleotide sequence complementary to a target RNA sequence or a portion thereof, and a second sequence having complementarity to said first sequence, wherein said second sequence comprises a terminal cap moiety at the 5'-end and 3'-end of said second sequence. In one
25 embodiment, each terminal cap moiety individually comprises an inverted abasic, inverted deoxy abasic, inverted nucleotide moiety, a group shown in **Figure 10**, an alkyl or cycloalkyl group, a heterocycle, or any other group that prevents RNAi activity in which the second sequence serves as a guide sequence or template for RNAi.

In one embodiment, the invention features a method for generating siNA
30 molecules of the invention with improved specificity for down regulating or inhibiting

the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising (a) introducing one or more chemical modifications into the structure of a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved specificity. In

5 another embodiment, the chemical modification used to improve specificity comprises terminal cap modifications at the 5'-end, 3'-end, or both 5' and 3'-ends of the siNA molecule. The terminal cap modifications can comprise, for example, structures shown in **Figure 10** (e.g. inverted deoxybasic moieties) or any other chemical modification that renders a portion of the siNA molecule (e.g. the sense strand) incapable of mediating

10 RNA interference against an off target nucleic acid sequence. In a non-limiting example, a siNA molecule is designed such that only the antisense sequence of the siNA molecule can serve as a guide sequence for RISC mediated degradation of a corresponding target RNA sequence. This can be accomplished by rendering the sense sequence of the siNA inactive by introducing chemical modifications to the sense strand that preclude

15 recognition of the sense strand as a guide sequence by RNAi machinery. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand of the siNA, or any other group that serves to render the sense strand inactive as a guide sequence for mediating RNA interference. These modifications, for example, can result in a molecule where the 5'-end of the sense strand no longer has a

20 free 5'-hydroxyl (5'-OH) or a free 5'-phosphate group (e.g., phosphate, diphosphate, triphosphate, cyclic phosphate etc.). Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19" and "Stab 17/22" chemistries and variants thereof (see Table IV) wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

25 In one embodiment, the invention features a method for generating siNA molecules of the invention with improved specificity for down regulating or inhibiting the expression of a target nucleic acid (e.g., a DNA or RNA such as a gene or its corresponding RNA), comprising introducing one or more chemical modifications into the structure of a siNA molecule that prevent a strand or portion of the siNA molecule

30 from acting as a template or guide sequence for RNAi activity. In one embodiment, the inactive strand or sense region of the siNA molecule is the sense strand or sense region of the siNA molecule, i.e. the strand or region of the siNA that does not have

complementarity to the target nucleic acid sequence. In one embodiment, such chemical modifications comprise any chemical group at the 5'-end of the sense strand or region of the siNA that does not comprise a 5'-hydroxyl (5'-OH) or 5'-phosphate group, or any other group that serves to render the sense strand or sense region inactive as a guide
5 sequence for mediating RNA interference. Non-limiting examples of such siNA constructs are described herein, such as "Stab 9/10", "Stab 7/8", "Stab 7/19" and "Stab 17/22" chemistries and variants thereof (see Table IV) wherein the 5'-end and 3'-end of the sense strand of the siNA do not comprise a hydroxyl group or phosphate group.

In one embodiment, the invention features a method for screening siNA molecules
10 that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of unmodified siNA molecules, (b) screening the siNA molecules of step (a) under conditions suitable for isolating siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence, and
15 (c) introducing chemical modifications (e.g. chemical modifications as described herein or as otherwise known in the art) into the active siNA molecules of (b). In one embodiment, the method further comprises re-screening the chemically modified siNA molecules of step (c) under conditions suitable for isolating chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

20 In one embodiment, the invention features a method for screening chemically modified siNA molecules that are active in mediating RNA interference against a target nucleic acid sequence comprising (a) generating a plurality of chemically modified siNA molecules (e.g. siNA molecules as described herein or as otherwise known in the art), and (b) screening the siNA molecules of step (a) under conditions suitable for isolating
25 chemically modified siNA molecules that are active in mediating RNA interference against the target nucleic acid sequence.

The term "ligand" refers to any compound or molecule, such as a drug, peptide, hormone, or neurotransmitter, that is capable of interacting with another compound, such as a receptor, either directly or indirectly. The receptor that interacts with a ligand can be
30 present on the surface of a cell or can alternately be an intercellular receptor. Interaction

of the ligand with the receptor can result in a biochemical reaction, or can simply be a physical interaction or association.

In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing an excipient formulation to a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability. Such excipients include polymers such as cyclodextrins, lipids, cationic lipids, polyamines, phospholipids, nanoparticles, receptors, ligands, and others.

In another embodiment, the invention features a method for generating siNA molecules of the invention with improved bioavailability comprising (a) introducing nucleotides having any of Formulae I-VII or any combination thereof into a siNA molecule, and (b) assaying the siNA molecule of step (a) under conditions suitable for isolating siNA molecules having improved bioavailability.

In another embodiment, polyethylene glycol (PEG) can be covalently attached to siNA compounds of the present invention. The attached PEG can be any molecular weight, preferably from about 2,000 to about 50,000 daltons (Da).

The present invention can be used alone or as a component of a kit having at least one of the reagents necessary to carry out the *in vitro* or *in vivo* introduction of RNA to test samples and/or subjects. For example, preferred components of the kit include a siNA molecule of the invention and a vehicle that promotes introduction of the siNA into cells of interest as described herein (e.g., using lipids and other methods of transfection known in the art, see for example Beigelman *et al.*, US 6,395,713). The kit can be used for target validation, such as in determining gene function and/or activity, or in drug optimization, and in drug discovery (see for example Usman *et al.*, USSN 60/402,996). Such a kit can also include instructions to allow a user of the kit to practice the invention.

The term "short interfering nucleic acid", "siNA", "short interfering RNA", "siRNA", "short interfering nucleic acid molecule", "short interfering oligonucleotide molecule", or "chemically-modified short interfering nucleic acid molecule" as used herein refers to any nucleic acid molecule capable of inhibiting or down regulating gene

expression or viral replication, for example by mediating RNA interference "RNAi" or gene silencing in a sequence-specific manner; see for example Zamore *et al.*, 2000, *Cell*, 101, 25-33; Bass, 2001, *Nature*, 411, 428-429; Elbashir *et al.*, 2001, *Nature*, 411, 494-498; and Kreutzer *et al.*, International PCT Publication No. WO 00/44895; Zernicka-Goetz *et al.*, International PCT Publication No. WO 01/36646; Fire, International PCT Publication No. WO 99/32619; Plaetinck *et al.*, International PCT Publication No. WO 00/01846; Mello and Fire, International PCT Publication No. WO 01/29058; Deschamps-Depaillette, International PCT Publication No. WO 99/07409; and Li *et al.*, International PCT Publication No. WO 00/44914; Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237; Hutvagner and Zamore, 2002, *Science*, 297, 2056-60; McManus *et al.*, 2002, *RNA*, 8, 842-850; Reinhart *et al.*, 2002, *Gene & Dev.*, 16, 1616-1626; and Reinhart & Bartel, 2002, *Science*, 297, 1831). Non limiting examples of siNA molecules of the invention are shown in **Figures 4-6**, and **Tables II and III** herein. For example the siNA can be a double-stranded polynucleotide molecule comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The siNA can be assembled from two separate oligonucleotides, where one strand is the sense strand and the other is the antisense strand, wherein the antisense and sense strands are self-complementary (i.e. each strand comprises nucleotide sequence that is complementary to nucleotide sequence in the other strand; such as where the antisense strand and sense strand form a duplex or double stranded structure, for example wherein the double stranded region is about 19 base pairs); the antisense strand comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense strand comprises nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. Alternatively, the siNA is assembled from a single oligonucleotide, where the self-complementary sense and antisense regions of the siNA are linked by means of a nucleic acid based or non-nucleic acid-based linker(s). The siNA can be a polynucleotide with a duplex, asymmetric duplex, hairpin or asymmetric hairpin secondary structure, having

self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a separate target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof. The

5 siNA can be a circular single-stranded polynucleotide having two or more loop structures and a stem comprising self-complementary sense and antisense regions, wherein the antisense region comprises nucleotide sequence that is complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof and the sense region having nucleotide sequence corresponding to the target nucleic acid sequence or a

10 portion thereof, and wherein the circular polynucleotide can be processed either *in vivo* or *in vitro* to generate an active siNA molecule capable of mediating RNAi. The siNA can also comprise a single stranded polynucleotide having nucleotide sequence complementary to nucleotide sequence in a target nucleic acid molecule or a portion thereof (for example, where such siNA molecule does not require the presence within the

15 siNA molecule of nucleotide sequence corresponding to the target nucleic acid sequence or a portion thereof), wherein the single stranded polynucleotide can further comprise a terminal phosphate group, such as a 5'-phosphate (see for example Martinez *et al.*, 2002, *Cell.*, 110, 563-574 and Schwarz *et al.*, 2002, *Molecular Cell*, 10, 537-568), or 5',3'-diphosphate. In certain embodiments, the siNA molecule of the invention comprises

20 separate sense and antisense sequences or regions, wherein the sense and antisense regions are covalently linked by nucleotide or non-nucleotide linkers molecules as is known in the art, or are alternately non-covalently linked by ionic interactions, hydrogen bonding, van der waals interactions, hydrophobic interactions, and/or stacking interactions. In certain embodiments, the siNA molecules of the invention comprise

25 nucleotide sequence that is complementary to nucleotide sequence of a target gene. In another embodiment, the siNA molecule of the invention interacts with nucleotide sequence of a target gene in a manner that causes inhibition of expression of the target gene. As used herein, siNA molecules need not be limited to those molecules containing only RNA, but further encompasses chemically-modified nucleotides and non-

30 nucleotides. In certain embodiments, the short interfering nucleic acid molecules of the invention lack 2'-hydroxy (2'-OH) containing nucleotides. Applicant describes in certain embodiments short interfering nucleic acids that do not require the presence of

nucleotides having a 2'-hydroxy group for mediating RNAi and as such, short interfering nucleic acid molecules of the invention optionally do not include any ribonucleotides (e.g., nucleotides having a 2'-OH group). Such siNA molecules that do not require the presence of ribonucleotides within the siNA molecule to support RNAi can however

5 have an attached linker or linkers or other attached or associated groups, moieties, or chains containing one or more nucleotides with 2'-OH groups. Optionally, siNA molecules can comprise ribonucleotides at about 5, 10, 20, 30, 40, or 50% of the nucleotide positions. The modified short interfering nucleic acid molecules of the invention can also be referred to as short interfering modified oligonucleotides "siMON."

10 As used herein, the term siNA is meant to be equivalent to other terms used to describe nucleic acid molecules that are capable of mediating sequence specific RNAi, for example short interfering RNA (siRNA), double-stranded RNA (dsRNA), micro-RNA (miRNA), short hairpin RNA (shRNA), short interfering oligonucleotide, short interfering nucleic acid, short interfering modified oligonucleotide, chemically-modified

15 siRNA, post-transcriptional gene silencing RNA (ptgsRNA), and others. In addition, as used herein, the term RNAi is meant to be equivalent to other terms used to describe sequence specific RNA interference, such as post transcriptional gene silencing, translational inhibition, or epigenetics. For example, siNA molecules of the invention can be used to epigenetically silence genes at both the post-transcriptional level or the

20 pre-transcriptional level. In a non-limiting example, epigenetic regulation of gene expression by siNA molecules of the invention can result from siNA mediated modification of chromatin structure to alter gene expression (see, for example, Verdel *et al.*, 2004, *Science*, 303, 672-676; Pal-Bhadra *et al.*, 2004, *Science*, 303, 669-672; Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-

25 2237).

In one embodiment, a siNA molecule of the invention is a duplex forming oligonucleotide "DFO", (see for example **Figures 14-15** and Vaish *et al.*, USSN 10/727,780 filed December 3, 2003).

30 In one embodiment, a siNA molecule of the invention is a multifunctional siNA, (see for example **Figures 16-22** and Jadhav *et al.*, USSN 60/543,480, filed February 10,

2004). The multifunctional siNA of the invention can comprise sequence targeting, for example, two regions of SARS RNA (see for example target sequences in **Tables II and III**) or alternately, SARS RNA and cellular RNA involved in SARS virus infection or replication. In another embodiment, a multifunctional siNA of the invention can
5 comprise sequence targeting for example both viral genes encoding RNAi inhibitory factors and viral genes encoding viral structural proteins.

By "asymmetric hairpin" as used herein is meant a linear siNA molecule comprising an antisense region, a loop portion that can comprise nucleotides or non-nucleotides, and a sense region that comprises fewer nucleotides than the antisense
10 region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and form a duplex with loop. For example, an asymmetric hairpin siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 (e.g.,
about 19, 20, 21, or 22) nucleotides) and a loop region comprising about 4 to about 8
15 (e.g., about 4, 5, 6, 7, or 8) nucleotides, and a sense region having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18) nucleotides that are complementary to the antisense region. The asymmetric hairpin siNA molecule can also comprise a 5'-terminal phosphate group that can be chemically modified. The loop
portion of the asymmetric hairpin siNA molecule can comprise nucleotides, non-
20 nucleotides, linker molecules, or conjugate molecules as described herein.

By "asymmetric duplex" as used herein is meant a siNA molecule having two separate strands comprising a sense region and an antisense region, wherein the sense region comprises fewer nucleotides than the antisense region to the extent that the sense region has enough complementary nucleotides to base pair with the antisense region and
25 form a duplex. For example, an asymmetric duplex siNA molecule of the invention can comprise an antisense region having length sufficient to mediate RNAi in a cell or in vitro system (e.g. about 19 to about 22 (e.g. about 19, 20, 21, or 22) nucleotides) and a sense region having about 3 to about 18 (e.g., about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,
15, 16, 17, or 18) nucleotides that are complementary to the antisense region.

30 By "modulate" is meant that the expression of the gene, or level of RNA molecule or equivalent RNA molecules encoding one or more proteins or protein subunits, or

activity of one or more proteins or protein subunits is up regulated or down regulated, such that expression, level, or activity is greater than or less than that observed in the absence of the modulator. For example, the term "modulate" can mean "inhibit," but the use of the word "modulate" is not limited to this definition.

5 By "inhibit", "down-regulate", or "reduce", it is meant that the expression of the gene, or level of RNA molecules or equivalent RNA molecules encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits, is reduced below that observed in the absence of the nucleic acid molecules (e.g., siNA) of the invention. In one embodiment, inhibition, down-regulation or reduction with an siNA
10 molecule is below that level observed in the presence of an inactive or attenuated molecule. In another embodiment, inhibition, down-regulation, or reduction with siNA molecules is below that level observed in the presence of, for example, an siNA molecule with scrambled sequence or with mismatches. In another embodiment, inhibition, down-regulation, or reduction of gene expression with a nucleic acid molecule
15 of the instant invention is greater in the presence of the nucleic acid molecule than in its absence.

By "gene", or "target gene", is meant, a nucleic acid that encodes an RNA, for example, nucleic acid sequences including, but not limited to, structural genes encoding a polypeptide. A gene or target gene can also encode a functional RNA (fRNA) or non-
20 coding RNA (ncRNA), such as small temporal RNA (stRNA), micro RNA (miRNA), small nuclear RNA (snRNA), short interfering RNA (siRNA), small nucleolar RNA (snRNA), ribosomal RNA (rRNA), transfer RNA (tRNA) and precursor RNAs thereof. Such non-coding RNAs can serve as target nucleic acid molecules for siNA mediated RNA interference in modulating the activity of fRNA or ncRNA involved in functional
25 or regulatory cellular processes. Abberant fRNA or ncRNA activity leading to disease can therefore be modulated by siNA molecules of the invention. siNA molecules targeting fRNA and ncRNA can also be used to manipulate or alter the genotype or phenotype of an organism or cell, by intervening in cellular processes such as genetic imprinting, transcription, translation, or nucleic acid processing (e.g., transamination,
30 methylation etc.). The target gene can be a gene derived from a cell, an endogenous gene, a transgene, or exogenous genes such as genes of a pathogen, for example a virus,

which is present in the cell after infection thereof. The cell containing the target gene can be derived from or contained in any organism, for example a plant, animal, protozoan, virus, bacterium, or fungus. Non-limiting examples of plants include monocots, dicots, or gymnosperms. Non-limiting examples of animals include
5 vertebrates or invertebrates. Non-limiting examples of fungi include molds or yeasts.

By "SARS" or "SARS virus" as used herein is meant the SARS virus or any protein, peptide, or polypeptide, having SARS virus activity or encoded by the SARS genome. The term "SARS" also includes nucleic acid molecules encoding RNA or protein(s) associated with the development and/or maintenance of SARS virus infection,
10 such as nucleic acid molecules which encode SARS RNA or polypeptides (such as polynucleotides having Genbank Accession numbers shown in Table I), including polypeptides of different strains of SARS, mutant SARS genes, and splice variants of SARS genes, as well as genes involved in SARS pathways of gene expression and/or SARS activity. Also, the term "SARS" is meant to encompass SARS viral gene products
15 and genes that modulate cellular targets for SARS virus infection, such as those described herein.

By "SARS protein" or "SARS virus protein" is meant, protein, peptide, or polypeptide, having SARS virus activity or encoded by the SARS genome or alternately, cellular proteins involved in SARS virus infection and/or replication.

By "homologous sequence" is meant, a nucleotide sequence that is shared by one or more polynucleotide sequences, such as genes, gene transcripts and/or non-coding polynucleotides. For example, a homologous sequence can be a nucleotide sequence that is shared by two or more genes encoding related but different proteins, such as different members of a gene family, different protein epitopes, different protein isoforms or
25 completely divergent genes, such as a cytokine and its corresponding receptors. A homologous sequence can be a nucleotide sequence that is shared by two or more non-coding polynucleotides, such as noncoding DNA or RNA, regulatory sequences, introns, and sites of transcriptional control or regulation. Homologous sequences can also include conserved sequence regions shared by more than one polynucleotide sequence.
30 Homology does not need to be perfect homology (e.g., 100%), as partially homologous sequences are also contemplated by the instant invention (e.g., 99%, 98%, 97%, 96%,

95%, 94%, 93%, 92%, 91%, 90%, 89%, 88%, 87%, 86%, 85%, 84%, 83%, 82%, 81%, 80% etc.).

By "conserved sequence region" is meant, a nucleotide sequence of one or more regions in a polynucleotide does not vary significantly between generations or from one biological system or organism to another biological system or organism. The polynucleotide can include both coding and non-coding DNA and RNA.

By "sense region" is meant a nucleotide sequence of a siNA molecule having complementarity to an antisense region of the siNA molecule. In addition, the sense region of a siNA molecule can comprise a nucleic acid sequence having homology with a target nucleic acid sequence.

By "antisense region" is meant a nucleotide sequence of a siNA molecule having complementarity to a target nucleic acid sequence. In addition, the antisense region of a siNA molecule can optionally comprise a nucleic acid sequence having complementarity to a sense region of the siNA molecule.

By "target nucleic acid" is meant any nucleic acid sequence whose expression or activity is to be modulated. The target nucleic acid can be DNA or RNA.

By "complementarity" is meant that a nucleic acid can form hydrogen bond(s) with another nucleic acid sequence by either traditional Watson-Crick or other non-traditional types. In reference to the nucleic molecules of the present invention, the binding free energy for a nucleic acid molecule with its complementary sequence is sufficient to allow the relevant function of the nucleic acid to proceed, e.g., RNAi activity. Determination of binding free energies for nucleic acid molecules is well known in the art (see, e.g., Turner *et al.*, 1987, *CSH Symp. Quant. Biol.* LII pp.123-133; Frier *et al.*, 1986, *Proc. Nat. Acad. Sci. USA* 83:9373-9377; Turner *et al.*, 1987, *J. Am. Chem. Soc.* 109:3783-3785). A percent complementarity indicates the percentage of contiguous residues in a nucleic acid molecule that can form hydrogen bonds (e.g., Watson-Crick base pairing) with a second nucleic acid sequence (e.g., 5, 6, 7, 8, 9, or 10 nucleotides out of a total of 10 nucleotides in the first oligonucleotide being base paired to a second nucleic acid sequence having 10 nucleotides represents 50%, 60%, 70%, 80%, 90%, and

100% complementary respectively). "Perfectly complementary" means that all the contiguous residues of a nucleic acid sequence will hydrogen bond with the same number of contiguous residues in a second nucleic acid sequence.

5 The siNA molecules of the invention represent a novel therapeutic approach to treat various diseases and conditions, including SARS virus infection, acute respiratory failure, viral pneumonia, and any other indications that can respond to the level of SARS in a cell or tissue. The reduction of SARS expression and thus reduction in the level of the respective protein relieves, to some extent, the symptoms of the disease or condition.

10 In one embodiment of the present invention, each sequence of a siNA molecule of the invention is independently about 18 to about 24 nucleotides in length, in specific embodiments about 18, 19, 20, 21, 22, 23, or 24 nucleotides in length. In another embodiment, the siNA duplexes of the invention independently comprise about 17 to about 23 base pairs (*e.g.*, about 17, 18, 19, 20, 21, 22 or 23). In yet another embodiment, siNA molecules of the invention comprising hairpin or circular structures are about 35 to about 55 (*e.g.*, about 35, 40, 45, 50 or 55) nucleotides in length, or about 38 to about 44 (*e.g.*, 38, 39, 40, 41, 42, 43 or 44) nucleotides in length and comprising about 16 to about 22 (*e.g.*, about 16, 17, 18, 19, 20, 21 or 22) base pairs. Exemplary siNA molecules of the invention are shown in **Table II**. Exemplary synthetic siNA molecules of the invention are shown in **Table III** and/or **Figures 4-5**.

20 As used herein "cell" is used in its usual biological sense, and does not refer to an entire multicellular organism, *e.g.*, specifically does not refer to a human. The cell can be present in an organism, *e.g.*, birds, plants and mammals such as humans, cows, sheep, apes, monkeys, swine, dogs, and cats. The cell can be prokaryotic (*e.g.*, bacterial cell) or eukaryotic (*e.g.*, mammalian or plant cell). The cell can be of somatic or germ line origin, totipotent or pluripotent, dividing or non-dividing. The cell can also be derived from or can comprise a gamete or embryo, a stem cell, or a fully differentiated cell.

30 The siNA molecules of the invention are added directly, or can be complexed with cationic lipids, packaged within liposomes, or otherwise delivered to target cells or tissues. The nucleic acid or nucleic acid complexes can be locally administered to relevant tissues *ex vivo*, or *in vivo* through injection, infusion pump or stent, with or

without their incorporation in biopolymers. In particular embodiments, the nucleic acid molecules of the invention comprise sequences shown in **Tables II-III** and/or **Figures 4-5**. Examples of such nucleic acid molecules consist essentially of sequences defined in these tables and figures. Furthermore, the chemically modified constructs described in **Table IV** can be applied to any siNA sequence of the invention.

In another aspect, the invention provides mammalian cells containing one or more siNA molecules of this invention. The one or more siNA molecules can independently be targeted to the same or different sites.

By "RNA" is meant a molecule comprising at least one ribonucleotide residue. By "ribonucleotide" is meant a nucleotide with a hydroxyl group at the 2' position of a β -D-ribo-furanose moiety. The terms include double-stranded RNA, single-stranded RNA, isolated RNA such as partially purified RNA, essentially pure RNA, synthetic RNA, recombinantly produced RNA, as well as altered RNA that differs from naturally occurring RNA by the addition, deletion, substitution and/or alteration of one or more nucleotides. Such alterations can include addition of non-nucleotide material, such as to the end(s) of the siNA or internally, for example at one or more nucleotides of the RNA. Nucleotides in the RNA molecules of the instant invention can also comprise non-standard nucleotides, such as non-naturally occurring nucleotides or chemically synthesized nucleotides or deoxynucleotides. These altered RNAs can be referred to as analogs or analogs of naturally-occurring RNA.

By "subject" is meant an organism, which is a donor or recipient of explanted cells or the cells themselves. "Subject" also refers to an organism to which the nucleic acid molecules of the invention can be administered. A subject can be a mammal or mammalian cells, including a human or human cells.

The term "phosphorothioate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise a sulfur atom. Hence, the term phosphorothioate refers to both phosphorothioate and phosphorodithioate internucleotide linkages.

The term "phosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z and/or W comprise an acetyl or protected acetyl group.

The term "thiophosphonoacetate" as used herein refers to an internucleotide linkage having Formula I, wherein Z comprises an acetyl or protected acetyl group and
5 W comprises a sulfur atom or alternately W comprises an acetyl or protected acetyl group and Z comprises a sulfur atom.

The term "universal base" as used herein refers to nucleotide base analogs that form base pairs with each of the natural DNA/RNA bases with little discrimination between them. Non-limiting examples of universal bases include C-phenyl, C-naphthyl
10 and other aromatic derivatives, inosine, azole carboxamides, and nitroazole derivatives such as 3-nitropyrrole, 4-nitroindole, 5-nitroindole, and 6-nitroindole as known in the art (see for example Loakes, 2001, *Nucleic Acids Research*, 29, 2437-2447).

The term "acyclic nucleotide" as used herein refers to any nucleotide having an acyclic ribose sugar, for example where any of the ribose carbons (C1, C2, C3, C4, or
15 C5), are independently or in combination absent from the nucleotide.

The nucleic acid molecules of the instant invention, individually, or in combination or in conjunction with other drugs, can be used to treat diseases or conditions discussed herein (e.g., cancers and othe proliferative conditions). For example, to treat a particular disease or condition, the siNA molecules can be administered to a subject or can be
20 administered to other appropriate cells evident to those skilled in the art, individually or in combination with one or more drugs under conditions suitable for the treatment.

In a further embodiment, the siNA molecules can be used in combination with other known treatments to treat conditions or diseases discussed above. For example, the described molecules could be used in combination with one or more known therapeutic
25 agents to treat a disease or condition. Non-limiting examples of other therapeutic agents that can be readily combined with a siNA molecule of the invention are enzymatic nucleic acid molecules, allosteric nucleic acid molecules, antisense, decoy, or aptamer nucleic acid molecules, antibodies such as monoclonal antibodies, small molecules, and other organic and/or inorganic compounds including metals, salts and ions.

In one embodiment, the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the invention, in a manner which allows expression of the siNA molecule. For example, the vector can contain sequence(s) encoding both strands of a siNA molecule comprising a duplex. The vector
5 can also contain sequence(s) encoding a single nucleic acid molecule that is self-complementary and thus forms a siNA molecule. Non-limiting examples of such expression vectors are described in Paul *et al.*, 2002, *Nature Biotechnology*, 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology*, 19, 497; Lee *et al.*, 2002, *Nature Biotechnology*, 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online
10 publication doi:10.1038/nm725.

In another embodiment, the invention features a mammalian cell, for example, a human cell, including an expression vector of the invention.

In yet another embodiment, the expression vector of the invention comprises a sequence for a siNA molecule having complementarity to a RNA molecule referred to by
15 a Genbank Accession numbers, for example Genbank Accession Nos. shown in **Table I**.

In one embodiment, an expression vector of the invention comprises a nucleic acid sequence encoding two or more siNA molecules, which can be the same or different.

In another aspect of the invention, siNA molecules that interact with target RNA molecules and down-regulate gene encoding target RNA molecules (for example target
20 RNA molecules referred to by Genbank Accession numbers herein) are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as
25 described herein, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of siNA molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecules bind and down-regulate gene function or expression via RNA interference (RNAi). Delivery of siNA expressing vectors can be systemic, such as by intravenous or intramuscular administration, by
30 administration to target cells ex-planted from a subject followed by reintroduction into

the subject, or by any other means that would allow for introduction into the desired target cell.

By "vectors" is meant any nucleic acid- and/or viral-based technique used to deliver a desired nucleic acid.

- 5 Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a non-limiting example of a scheme for the synthesis of siNA molecules. The complementary siNA sequence strands, strand 1 and strand 2, are synthesized in tandem and are connected by a cleavable linkage, such as a nucleotide succinate or abasic succinate, which can be the same or different from the cleavable linker used for solid phase synthesis on a solid support. The synthesis can be either solid phase or solution phase, in the example shown, the synthesis is a solid phase synthesis. The synthesis is performed such that a protecting group, such as a dimethoxytrityl group, remains intact on the terminal nucleotide of the tandem oligonucleotide. Upon cleavage and deprotection of the oligonucleotide, the two siNA strands spontaneously hybridize to form a siNA duplex, which allows the purification of the duplex by utilizing the properties of the terminal protecting group, for example by applying a trityl on purification method wherein only duplexes/oligonucleotides with the terminal protecting group are isolated.

Figure 2 shows a MALDI-TOF mass spectrum of a purified siNA duplex synthesized by a method of the invention. The two peaks shown correspond to the predicted mass of the separate siNA sequence strands. This result demonstrates that the siNA duplex generated from tandem synthesis can be purified as a single entity using a simple trityl-on purification methodology.

Figure 3 shows a non-limiting proposed mechanistic representation of target RNA degradation involved in RNAi. Double-stranded RNA (dsRNA), which is generated by RNA-dependent RNA polymerase (RdRP) from foreign single-stranded RNA, for example viral, transposon, or other exogenous RNA, activates the DICER enzyme that in

turn generates siNA duplexes. Alternately, synthetic or expressed siNA can be introduced directly into a cell by appropriate means. An active siNA complex forms which recognizes a target RNA, resulting in degradation of the target RNA by the RISC endonuclease complex or in the synthesis of additional RNA by RNA-dependent RNA polymerase (RdRP), which can activate DICER and result in additional siNA molecules, thereby amplifying the RNAi response.

Figure 4A-F shows non-limiting examples of chemically-modified siNA constructs of the present invention. In the figure, N stands for any nucleotide (adenosine, guanosine, cytosine, uridine, or optionally thymidine, for example thymidine can be substituted in the overhanging regions designated by parenthesis (N N). Various modifications are shown for the sense and antisense strands of the siNA constructs.

Figure 4A: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all nucleotides present are ribonucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4B: The sense strand comprises 21 nucleotides wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all

pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified
5 internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the sense and antisense strand.

Figure 4C: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and
10 wherein all pyrimidine nucleotides that may be present are 2'-O-methyl or 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally
15 complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as
20 described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4D: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified
25 nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the
30 target RNA sequence, wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are

2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown
5 as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4E: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides,
10 deoxynucleotides, universal bases, or other chemical modifications described herein. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides and all purine nucleotides that may be present are
15 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand.

Figure 4F: The sense strand comprises 21 nucleotides having 5'- and 3'- terminal cap moieties wherein the two terminal 3'-nucleotides are optionally base paired and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro modified nucleotides except for (N N) nucleotides, which can comprise ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein and
25 wherein and all purine nucleotides that may be present are 2'-deoxy nucleotides. The antisense strand comprises 21 nucleotides, optionally having a 3'-terminal glyceryl moiety and wherein the two terminal 3'-nucleotides are optionally complementary to the target RNA sequence, and having one 3'-terminal phosphorothioate internucleotide linkage and wherein all pyrimidine nucleotides that may be present are 2'-deoxy-2'-fluoro
30 modified nucleotides and all purine nucleotides that may be present are 2'-deoxy nucleotides except for (N N) nucleotides, which can comprise ribonucleotides,

deoxynucleotides, universal bases, or other chemical modifications described herein. A modified internucleotide linkage, such as a phosphorothioate, phosphorodithioate or other modified internucleotide linkage as described herein, shown as "s", optionally connects the (N N) nucleotides in the antisense strand. The antisense strand of constructs A-F comprise sequence complementary to any target nucleic acid sequence of the invention. Furthermore, when a glyceryl moiety (L) is present at the 3'-end of the antisense strand for any construct shown in Figure 4 A-F, the modified internucleotide linkage is optional.

Figure 5A-F shows non-limiting examples of specific chemically-modified siNA sequences of the invention. A-F applies the chemical modifications described in **Figure 4A-F** to a SARS virus siNA sequence. Such chemical modifications can be applied to any SARS sequence and/or SARS polymorphism sequence.

Figure 6 shows non-limiting examples of different siNA constructs of the invention. The examples shown (constructs 1, 2, and 3) have 19 representative base pairs; however, different embodiments of the invention include any number of base pairs described herein. Bracketed regions represent nucleotide overhangs, for example comprising about 1, 2, 3, or 4 nucleotides in length, preferably about 2 nucleotides. Constructs 1 and 2 can be used independently for RNAi activity. Construct 2 can comprise a polynucleotide or non-nucleotide linker, which can optionally be designed as a biodegradable linker. In one embodiment, the loop structure shown in construct 2 can comprise a biodegradable linker that results in the formation of construct 1 *in vivo* and/or *in vitro*. In another example, construct 3 can be used to generate construct 2 under the same principle wherein a linker is used to generate the active siNA construct 2 *in vivo* and/or *in vitro*, which can optionally utilize another biodegradable linker to generate the active siNA construct 1 *in vivo* and/or *in vitro*. As such, the stability and/or activity of the siNA constructs can be modulated based on the design of the siNA construct for use *in vivo* or *in vitro* and/or *in vitro*.

Figure 7A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate siNA hairpin constructs.

Figure 7A: A DNA oligomer is synthesized with a 5'-restriction site (R1) sequence followed by a region having sequence identical (sense region of siNA) to a predetermined SARS target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, which is followed by a loop sequence of defined sequence (X), comprising, for example, about 3 to about 10 nucleotides.

Figure 7B: The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence that will result in a siNA transcript having specificity for a SARS target sequence and having self-complementary sense and antisense regions.

Figure 7C: The construct is heated (for example to about 95°C) to linearize the sequence, thus allowing extension of a complementary second DNA strand using a primer to the 3'-restriction sequence of the first strand. The double-stranded DNA is then inserted into an appropriate vector for expression in cells. The construct can be designed such that a 3'-terminal nucleotide overhang results from the transcription, for example by engineering restriction sites and/or utilizing a poly-U termination region as described in Paul *et al.*, 2002, *Nature Biotechnology*, 29, 505-508.

Figure 8A-C is a diagrammatic representation of a scheme utilized in generating an expression cassette to generate double-stranded siNA constructs.

Figure 8A: A DNA oligomer is synthesized with a 5'-restriction (R1) site sequence followed by a region having sequence identical (sense region of siNA) to a predetermined SARS target sequence, wherein the sense region comprises, for example, about 19, 20, 21, or 22 nucleotides (N) in length, and which is followed by a 3'-restriction site (R2) which is adjacent to a loop sequence of defined sequence (X).

Figure 8B: The synthetic construct is then extended by DNA polymerase to generate a hairpin structure having self-complementary sequence.

Figure 8C: The construct is processed by restriction enzymes specific to R1 and R2 to generate a double-stranded DNA which is then inserted into an appropriate vector for expression in cells. The transcription cassette is designed such that a U6 promoter region flanks each side of the dsDNA which generates the separate sense and antisense

strands of the siNA. Poly T termination sequences can be added to the constructs to generate U overhangs in the resulting transcript.

Figure 9A-E is a diagrammatic representation of a method used to determine target sites for siNA mediated RNAi within a particular target nucleic acid sequence, such as messenger RNA.

Figure 9A: A pool of siNA oligonucleotides are synthesized wherein the antisense region of the siNA constructs has complementarity to target sites across the target nucleic acid sequence, and wherein the sense region comprises sequence complementary to the antisense region of the siNA.

Figure 9B&C: (Figure 9B) The sequences are pooled and are inserted into vectors such that **(Figure 9C)** transfection of a vector into cells results in the expression of the siNA.

Figure 9D: Cells are sorted based on phenotypic change that is associated with modulation of the target nucleic acid sequence.

Figure 9E: The siNA is isolated from the sorted cells and is sequenced to identify efficacious target sites within the target nucleic acid sequence.

Figure 10 shows non-limiting examples of different stabilization chemistries (1-10) that can be used, for example, to stabilize the 3'-end of siNA sequences of the invention, including (1) [3-3']-inverted deoxyribose; (2) deoxyribonucleotide; (3) [5'-3']-3'-deoxyribonucleotide; (4) [5'-3']-ribonucleotide; (5) [5'-3']-3'-O-methyl ribonucleotide; (6) 3'-glyceryl; (7) [3'-5']-3'-deoxyribonucleotide; (8) [3'-3']-deoxyribonucleotide; (9) [5'-2']-deoxyribonucleotide; and (10) [5-3']-dideoxyribonucleotide. In addition to modified and unmodified backbone chemistries indicated in the figure, these chemistries can be combined with different backbone modifications as described herein, for example, backbone modifications having Formula I. In addition, the 2'-deoxy nucleotide shown 5' to the terminal modifications shown can be another modified or unmodified nucleotide or non-nucleotide described herein, for example modifications having any of Formulae I-VII or any combination thereof.

Figure 11 shows a non-limiting example of a strategy used to identify chemically modified siNA constructs of the invention that are nuclease resistance while preserving the ability to mediate RNAi activity. Chemical modifications are introduced into the siNA construct based on educated design parameters (e.g. introducing 2'-modifications, base modifications, backbone modifications, terminal cap modifications etc). The modified construct is tested in an appropriate system (e.g. human serum for nuclease resistance, shown, or an animal model for PK/delivery parameters). In parallel, the siNA construct is tested for RNAi activity, for example in a cell culture system such as a luciferase reporter assay). Lead siNA constructs are then identified which possess a particular characteristic while maintaining RNAi activity, and can be further modified and assayed once again. This same approach can be used to identify siNA-conjugate molecules with improved pharmacokinetic profiles, delivery, and RNAi activity.

Figure 12 shows non-limiting examples of phosphorylated siNA molecules of the invention, including linear and duplex constructs and asymmetric derivatives thereof.

Figure 13 shows non-limiting examples of chemically modified terminal phosphate groups of the invention.

Figure 14A shows a non-limiting example of methodology used to design self complementary DFO constructs utilizing palidrome and/or repeat nucleic acid sequences that are identified in a target nucleic acid sequence. (i) A palidrome or repeat sequence is identified in a nucleic acid target sequence. (ii) A sequence is designed that is complementary to the target nucleic acid sequence and the palidrome sequence. (iii) An inverse repeat sequence of the non-palidrome/repeat portion of the complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complimentary DFO molecule comprising sequence complementary to the nucleic acid target. (iv) The DFO molecule can self-assemble to form a double stranded oligonucleotide. **Figure 14B** shows a non-limiting representative example of a duplex forming oligonucleotide sequence. **Figure 14C** shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence. **Figure 14D** shows a non-limiting example of the self assembly schematic of a representative duplex forming oligonucleotide sequence followed by interaction with a target nucleic acid sequence resulting in modulation of gene expression.

Figure 15 shows a non-limiting example of the design of self complementary DFO constructs utilizing palidrome and/or repeat nucleic acid sequences that are incorporated into the DFO constructs that have sequence complementary to any target nucleic acid sequence of interest. Incorporation of these palidrome/repeat sequences allow the design of DFO constructs that form duplexes in which each strand is capable of mediating modulation of target gene expression, for example by RNAi. First, the target sequence is identified. A complementary sequence is then generated in which nucleotide or non-nucleotide modifications (shown as X or Y) are introduced into the complementary sequence that generate an artificial palidrome (shown as XYXYXY in the Figure). An inverse repeat of the non-palidrome/repeat complementary sequence is appended to the 3'-end of the complementary sequence to generate a self complimentary DFO comprising sequence complementary to the nucleic acid target. The DFO can self-assemble to form a double stranded oligonucleotide.

Figure 16 shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. **Figure 16A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 16B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 17 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences. **Figure 17A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 17B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in **Figure 16**.

Figure 18 shows non-limiting examples of multifunctional siNA molecules of the invention comprising two separate polynucleotide sequences that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifunctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. **Figure 18A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 3'-ends of each polynucleotide sequence in the multifunctional siNA, and

wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 18B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first and second complementary regions are situated at the 5'-ends of each polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences.

Figure 19 shows non-limiting examples of multifunctional siNA molecules of the invention comprising a single polynucleotide sequence comprising distinct regions that are each capable of mediating RNAi directed cleavage of differing target nucleic acid sequences and wherein the multifunctional siNA construct further comprises a self complementary, palindrome, or repeat region, thus enabling shorter bifunctional siNA constructs that can mediate RNA interference against differing target nucleic acid sequences. **Figure 19A** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the second complementary region is situated at the 3'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. **Figure 19B** shows a non-limiting example of a multifunctional siNA molecule having a first region that is complementary to a first target nucleic acid sequence (complementary region 1) and a

second region that is complementary to a second target nucleic acid sequence (complementary region 2), wherein the first complementary region is situated at the 5'-end of the polynucleotide sequence in the multifunctional siNA, and wherein the first and second complementary regions further comprise a self complementary, palindrome, or repeat region. The dashed portions of each polynucleotide sequence of the multifunctional siNA construct have complementarity with regard to corresponding portions of the siNA duplex, but do not have complementarity to the target nucleic acid sequences. In one embodiment, these multifunctional siNA constructs are processed in vivo or in vitro to generate multifunctional siNA constructs as shown in **Figure 18**.

Figure 20 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid molecules, such as separate RNA molecules encoding differing proteins, for example, differing viral strains, a virus and a cellular protein involved in viral infection or replication, or differing proteins involved in a common or divergent biologic pathway that is implicated in the maintenance of progression of disease. Each strand of the multifunctional siNA construct comprises a region having complementarity to separate target nucleic acid molecules. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interference mediated cleavage of its corresponding target. These design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.*, 2003, *Cell*, 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide positions as is known in the art.

Figure 21 shows a non-limiting example of how multifunctional siNA molecules of the invention can target two separate target nucleic acid sequences within the same target nucleic acid molecule, such as alternate coding regions of a RNA, coding and non-coding regions of a RNA, or alternate splice variant regions of a RNA. Each strand of the multifunctional siNA construct comprises a region having complementarity to the separate regions of the target nucleic acid molecule. The multifunctional siNA molecule is designed such that each strand of the siNA can be utilized by the RISC complex to initiate RNA interference mediated cleavage of its corresponding target region. These

design parameters can include destabilization of each end of the siNA construct (see for example Schwarz *et al.*, 2003, *Cell*, 115, 199-208). Such destabilization can be accomplished for example by using guanosine-cytidine base pairs, alternate base pairs (e.g., wobbles), or destabilizing chemically modified nucleotides at terminal nucleotide
5 positions as is known in the art.

DETAILED DESCRIPTION OF THE INVENTION

Mechanism of Action of Nucleic Acid Molecules of the Invention

The discussion that follows discusses the proposed mechanism of RNA
10 interference mediated by short interfering RNA as is presently known, and is not meant to be limiting and is not an admission of prior art. Applicant demonstrates herein that chemically-modified short interfering nucleic acids possess similar or improved capacity to mediate RNAi as do siRNA molecules and are expected to possess improved stability and activity *in vivo*; therefore, this discussion is not meant to be limiting only to siRNA
15 and can be applied to siNA as a whole. By "improved capacity to mediate RNAi" or "improved RNAi activity" is meant to include RNAi activity measured *in vitro* and/or *in vivo* where the RNAi activity is a reflection of both the ability of the siNA to mediate RNAi and the stability of the siNAs of the invention. In this invention, the product of these activities can be increased *in vitro* and/or *in vivo* compared to an all RNA siRNA
20 or a siNA containing a plurality of ribonucleotides. In some cases, the activity or stability of the siNA molecule can be decreased (i.e., less than ten-fold), but the overall activity of the siNA molecule is enhanced *in vitro* and/or *in vivo*.

RNA interference refers to the process of sequence specific post-transcriptional gene silencing in animals mediated by short interfering RNAs (siRNAs) (Fire *et al.*,
25 1998, *Nature*, 391, 806). The corresponding process in plants is commonly referred to as post-transcriptional gene silencing or RNA silencing and is also referred to as quelling in fungi. The process of post-transcriptional gene silencing is thought to be an evolutionarily-conserved cellular defense mechanism used to prevent the expression of foreign genes which is commonly shared by diverse flora and phyla (Fire *et al.*, 1999,

Trends Genet., 15, 358). Such protection from foreign gene expression may have evolved in response to the production of double-stranded RNAs (dsRNAs) derived from viral infection or the random integration of transposon elements into a host genome via a cellular response that specifically destroys homologous single-stranded RNA or viral genomic RNA. The presence of dsRNA in cells triggers the RNAi response through a mechanism that has yet to be fully characterized. This mechanism appears to be different from the interferon response that results from dsRNA-mediated activation of protein kinase PKR and 2', 5'-oligoadenylate synthetase resulting in non-specific cleavage of mRNA by ribonuclease L.

10 The presence of long dsRNAs in cells stimulates the activity of a ribonuclease III enzyme referred to as Dicer. Dicer is involved in the processing of the dsRNA into short pieces of dsRNA known as short interfering RNAs (siRNAs) (Berstein *et al.*, 2001, *Nature*, 409, 363). Short interfering RNAs derived from Dicer activity are typically about 21 to about 23 nucleotides in length and comprise about 19 base pair duplexes.

15 Dicer has also been implicated in the excision of 21- and 22-nucleotide small temporal RNAs (stRNAs) from precursor RNA of conserved structure that are implicated in translational control (Hutvagner *et al.*, 2001, *Science*, 293, 834). The RNAi response also features an endonuclease complex containing a siRNA, commonly referred to as an RNA-induced silencing complex (RISC), which mediates cleavage of single-stranded

20 RNA having sequence homologous to the siRNA. Cleavage of the target RNA takes place in the middle of the region complementary to the guide sequence of the siRNA duplex (Elbashir *et al.*, 2001, *Genes Dev.*, 15, 188). In addition, RNA interference can also involve small RNA (e.g., micro-RNA or miRNA) mediated gene silencing, presumably through cellular mechanisms that regulate chromatin structure and thereby

25 prevent transcription of target gene sequences (see for example Allshire, 2002, *Science*, 297, 1818-1819; Volpe *et al.*, 2002, *Science*, 297, 1833-1837; Jenuwein, 2002, *Science*, 297, 2215-2218; and Hall *et al.*, 2002, *Science*, 297, 2232-2237). As such, siRNA molecules of the invention can be used to mediate gene silencing via interaction with RNA transcripts or alternately by interaction with particular gene sequences, wherein

30 such interaction results in gene silencing either at the transcriptional level or post-transcriptional level.

RNAi has been studied in a variety of systems. Fire *et al.*, 1998, *Nature*, 391, 806, were the first to observe RNAi in *C. elegans*. Wianny and Goetz, 1999, *Nature Cell Biol.*, 2, 70, describe RNAi mediated by dsRNA in mouse embryos. Hammond *et al.*, 2000, *Nature*, 404, 293, describe RNAi in *Drosophila* cells transfected with dsRNA.

5 Elbashir *et al.*, 2001, *Nature*, 411, 494, describe RNAi induced by introduction of duplexes of synthetic 21-nucleotide RNAs in cultured mammalian cells including human embryonic kidney and HeLa cells. Recent work in *Drosophila* embryonic lysates has revealed certain requirements for siRNA length, structure, chemical composition, and sequence that are essential to mediate efficient RNAi activity. These studies have shown

10 that 21 nucleotide siRNA duplexes are most active when containing two 2-nucleotide 3'-terminal nucleotide overhangs. Furthermore, substitution of one or both siRNA strands with 2'-deoxy or 2'-O-methyl nucleotides abolishes RNAi activity, whereas substitution of 3'-terminal siRNA nucleotides with deoxy nucleotides was shown to be tolerated. Mismatch sequences in the center of the siRNA duplex were also shown to abolish RNAi

15 activity. In addition, these studies also indicate that the position of the cleavage site in the target RNA is defined by the 5'-end of the siRNA guide sequence rather than the 3'-end (Elbashir *et al.*, 2001, *EMBO J.*, 20, 6877). Other studies have indicated that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA activity and that ATP is utilized to maintain the 5'-phosphate moiety on the siRNA

20 (Nykanen *et al.*, 2001, *Cell*, 107, 309); however, siRNA molecules lacking a 5'-phosphate are active when introduced exogenously, suggesting that 5'-phosphorylation of siRNA constructs may occur *in vivo*.

Synthesis of Nucleic acid Molecules

Synthesis of nucleic acids greater than 100 nucleotides in length is difficult using

25 automated methods, and the therapeutic cost of such molecules is prohibitive. In this invention, small nucleic acid motifs ("small" refers to nucleic acid motifs no more than 100 nucleotides in length, preferably no more than 80 nucleotides in length, and most preferably no more than 50 nucleotides in length; *e.g.*, individual siNA oligonucleotide sequences or siNA sequences synthesized in tandem) are preferably used for exogenous

30 delivery. The simple structure of these molecules increases the ability of the nucleic acid

to invade targeted regions of protein and/or RNA structure. Exemplary molecules of the instant invention are chemically synthesized, and others can similarly be synthesized.

Oligonucleotides (e.g., certain modified oligonucleotides or portions of oligonucleotides lacking ribonucleotides) are synthesized using protocols known in the art, for example as described in Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19, Thompson *et al.*, International PCT Publication No. WO 99/54459, Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684, Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, Brennan *et al.*, 1998, *Biotechnol Bioeng.*, 61, 33-45, and Brennan, U.S. Pat. No. 6,001,311. All of these references are incorporated herein by reference. The synthesis of oligonucleotides makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 μmol scale protocol with a 2.5 min coupling step for 2'-O-methylated nucleotides and a 45 second coupling step for 2'-deoxy nucleotides or 2'-deoxy-2'-fluoro nucleotides. Table V outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 μmol scale can be performed on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 μL of 0.11 M = 6.6 μmol) of 2'-O-methyl phosphoramidite and a 105-fold excess of S-ethyl tetrazole (60 μL of 0.25 M = 15 μmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 22-fold excess (40 μL of 0.11 M = 4.4 μmol) of deoxy phosphoramidite and a 70-fold excess of S-ethyl tetrazole (40 μL of 0.25 M = 10 μmol) can be used in each coupling cycle of deoxy residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc. synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems, Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); and oxidation solution is 16.9 mM I_2 , 49 mM pyridine, 9% water in THF (PerSeptive Biosystems, Inc.). Burdick & Jackson Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained

from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide, 0.05 M in acetonitrile) is used.

Deprotection of the DNA-based oligonucleotides is performed as follows: the
5 polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aqueous methylamine (1 mL) at 65 °C for 10 minutes. After cooling to -20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of EtOH:MeCN:H₂O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants,
10 containing the oligoribonucleotide, are dried to a white powder.

The method of synthesis used for RNA including certain siNA molecules of the invention follows the procedure as described in Usman *et al.*, 1987, *J. Am. Chem. Soc.*, 109, 7845; Scaringe *et al.*, 1990, *Nucleic Acids Res.*, 18, 5433; and Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677-2684 Wincott *et al.*, 1997, *Methods Mol. Bio.*, 74, 59, and
15 makes use of common nucleic acid protecting and coupling groups, such as dimethoxytrityl at the 5'-end, and phosphoramidites at the 3'-end. In a non-limiting example, small scale syntheses are conducted on a 394 Applied Biosystems, Inc. synthesizer using a 0.2 µmol scale protocol with a 7.5 min coupling step for alkylsilyl protected nucleotides and a 2.5 min coupling step for 2'-O-methylated nucleotides.
20 **Table V** outlines the amounts and the contact times of the reagents used in the synthesis cycle. Alternatively, syntheses at the 0.2 µmol scale can be done on a 96-well plate synthesizer, such as the instrument produced by Protogene (Palo Alto, CA) with minimal modification to the cycle. A 33-fold excess (60 µL of 0.11 M = 6.6 µmol) of 2'-O-methyl phosphoramidite and a 75-fold excess of S-ethyl tetrazole (60 µL of 0.25 M = 15
25 µmol) can be used in each coupling cycle of 2'-O-methyl residues relative to polymer-bound 5'-hydroxyl. A 66-fold excess (120 µL of 0.11 M = 13.2 µmol) of alkylsilyl (ribo) protected phosphoramidite and a 150-fold excess of S-ethyl tetrazole (120 µL of 0.25 M = 30 µmol) can be used in each coupling cycle of ribo residues relative to polymer-bound 5'-hydroxyl. Average coupling yields on the 394 Applied Biosystems, Inc.
30 synthesizer, determined by colorimetric quantitation of the trityl fractions, are typically 97.5-99%. Other oligonucleotide synthesis reagents for the 394 Applied Biosystems,

- Inc. synthesizer include the following: detritylation solution is 3% TCA in methylene chloride (ABI); capping is performed with 16% *N*-methyl imidazole in THF (ABI) and 10% acetic anhydride/10% 2,6-lutidine in THF (ABI); oxidation solution is 16.9 mM I₂, 49 mM pyridine, 9% water in THF (PerSeptive Biosystems, Inc.).
- 5 Synthesis Grade acetonitrile is used directly from the reagent bottle. S-Ethyltetrazole solution (0.25 M in acetonitrile) is made up from the solid obtained from American International Chemical, Inc. Alternately, for the introduction of phosphorothioate linkages, Beaucage reagent (3H-1,2-Benzodithiol-3-one 1,1-dioxide 0.05 M in acetonitrile) is used.
- 10 Deprotection of the RNA is performed using either a two-pot or one-pot protocol. For the two-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 40% aq. methylamine (1 mL) at 65 °C for 10 min. After cooling to -20 °C, the supernatant is removed from the polymer support. The support is washed three times with 1.0 mL of
- 15 EtOH:MeCN:H₂O/3:1:1, vortexed and the supernatant is then added to the first supernatant. The combined supernatants, containing the oligoribonucleotide, are dried to a white powder. The base deprotected oligoribonucleotide is resuspended in anhydrous TEA/HF/NMP solution (300 µL of a solution of 1.5 mL *N*-methylpyrrolidinone, 750 µL TEA and 1 mL TEA•3HF to provide a 1.4 M HF concentration) and heated to 65 °C.
- 20 After 1.5 h, the oligomer is quenched with 1.5 M NH₄HCO₃.

Alternatively, for the one-pot protocol, the polymer-bound trityl-on oligoribonucleotide is transferred to a 4 mL glass screw top vial and suspended in a solution of 33% ethanolic methylamine/DMSO: 1/1 (0.8 mL) at 65 °C for 15 minutes. The vial is brought to room temperature TEA•3HF (0.1 mL) is added and the vial is

25 heated at 65 °C for 15 minutes. The sample is cooled at -20 °C and then quenched with 1.5 M NH₄HCO₃.

For purification of the trityl-on oligomers, the quenched NH₄HCO₃ solution is loaded onto a C-18 containing cartridge that had been prewashed with acetonitrile followed by 50 mM TEAA. After washing the loaded cartridge with water, the RNA is

30 detritylated with 0.5% TFA for 13 minutes. The cartridge is then washed again with

water, salt exchanged with 1 M NaCl and washed with water again. The oligonucleotide is then eluted with 30% acetonitrile.

The average stepwise coupling yields are typically >98% (Wincott *et al.*, 1995 *Nucleic Acids Res.* 23, 2677-2684). Those of ordinary skill in the art will recognize that
5 the scale of synthesis can be adapted to be larger or smaller than the example described above including but not limited to 96-well format.

Alternatively, the nucleic acid molecules of the present invention can be synthesized separately and joined together post-synthetically, for example, by ligation (Moore *et al.*, 1992, *Science* 256, 9923; Draper *et al.*, International PCT publication No.
10 WO 93/23569; Shabarova *et al.*, 1991, *Nucleic Acids Research* 19, 4247; Bellon *et al.*, 1997, *Nucleosides & Nucleotides*, 16, 951; Bellon *et al.*, 1997, *Bioconjugate Chem.* 8, 204), or by hybridization following synthesis and/or deprotection.

The siNA molecules of the invention can also be synthesized via a tandem synthesis methodology as described in Example 1 herein, wherein both siNA strands are
15 synthesized as a single contiguous oligonucleotide fragment or strand separated by a cleavable linker which is subsequently cleaved to provide separate siNA fragments or strands that hybridize and permit purification of the siNA duplex. The linker can be a polynucleotide linker or a non-nucleotide linker. The tandem synthesis of siNA as described herein can be readily adapted to both multiwell/multiplate synthesis platforms
20 such as 96 well or similarly larger multi-well platforms. The tandem synthesis of siNA as described herein can also be readily adapted to large scale synthesis platforms employing batch reactors, synthesis columns and the like.

A siNA molecule can also be assembled from two distinct nucleic acid strands or fragments wherein one fragment includes the sense region and the second fragment
25 includes the antisense region of the RNA molecule.

The nucleic acid molecules of the present invention can be modified extensively to enhance stability by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-H (for a review see Usman and Cedergren, 1992, *TIBS* 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163). siNA constructs can

be purified by gel electrophoresis using general methods or can be purified by high pressure liquid chromatography (HPLC; see Wincott *et al.*, *supra*, the totality of which is hereby incorporated herein by reference) and re-suspended in water.

5 In another aspect of the invention, siNA molecules of the invention are expressed from transcription units inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. The recombinant vectors capable of expressing the siNA molecules can be delivered as described herein, and persist in target cells. Alternatively, viral vectors can be used that
10 provide for transient expression of siNA molecules.

Optimizing Activity of the nucleic acid molecule of the invention.

Chemically synthesizing nucleic acid molecules with modifications (base, sugar and/or phosphate) can prevent their degradation by serum ribonucleases, which can increase their potency (see *e.g.*, Eckstein *et al.*, International Publication No. WO
15 92/07065; Perrault *et al.*, 1990 *Nature* 344, 565; Pieken *et al.*, 1991, *Science* 253, 314; Usman and Cedergren, 1992, *Trends in Biochem. Sci.* 17, 334; Usman *et al.*, International Publication No. WO 93/15187; and Rossi *et al.*, International Publication No. WO 91/03162; Sproat, U.S. Pat. No. 5,334,711; Gold *et al.*, U.S. Pat. No. 6,300,074; and Burgin *et al.*, *supra*; all of which are incorporated by reference herein). All of the
20 above references describe various chemical modifications that can be made to the base, phosphate and/or sugar moieties of the nucleic acid molecules described herein. Modifications that enhance their efficacy in cells, and removal of bases from nucleic acid molecules to shorten oligonucleotide synthesis times and reduce chemical requirements are desired.

25 There are several examples in the art describing sugar, base and phosphate modifications that can be introduced into nucleic acid molecules with significant enhancement in their nuclease stability and efficacy. For example, oligonucleotides are modified to enhance stability and/or enhance biological activity by modification with nuclease resistant groups, for example, 2'-amino, 2'-C-allyl, 2'-fluoro, 2'-O-methyl, 2'-O-
30 allyl, 2'-H, nucleotide base modifications (for a review see Usman and Cedergren, 1992,

TIBS. 17, 34; Usman *et al.*, 1994, *Nucleic Acids Symp. Ser.* 31, 163; Burgin *et al.*, 1996, *Biochemistry*, 35, 14090). Sugar modification of nucleic acid molecules have been extensively described in the art (see Eckstein *et al.*, *International Publication* PCT No. WO 92/07065; Perrault *et al.* *Nature*, 1990, 344, 565-568; Pieken *et al.* *Science*, 1991, 5 253, 314-317; Usman and Cedergren, *Trends in Biochem. Sci.*, 1992, 17, 334-339; Usman *et al.* *International Publication* PCT No. WO 93/15187; Sproat, *U.S. Pat.* No. 5,334,711 and Beigelman *et al.*, 1995, *J. Biol. Chem.*, 270, 25702; Beigelman *et al.*, International PCT publication No. WO 97/26270; Beigelman *et al.*, *U.S. Pat.* No. 5,716,824; Usman *et al.*, *U.S. Pat.* No. 5,627,053; Woolf *et al.*, International PCT 10 Publication No. WO 98/13526; Thompson *et al.*, *USSN* 60/082,404 which was filed on April 20, 1998; Karpeisky *et al.*, 1998, *Tetrahedron Lett.*, 39, 1131; Earnshaw and Gait, 1998, *Biopolymers (Nucleic Acid Sciences)*, 48, 39-55; Verma and Eckstein, 1998, *Annu. Rev. Biochem.*, 67, 99-134; and Burlina *et al.*, 1997, *Bioorg. Med. Chem.*, 5, 1999-2010; all of the references are hereby incorporated in their totality by reference herein). Such 15 publications describe general methods and strategies to determine the location of incorporation of sugar, base and/or phosphate modifications and the like into nucleic acid molecules without modulating catalysis, and are incorporated by reference herein. In view of such teachings, similar modifications can be used as described herein to modify the siNA nucleic acid molecules of the instant invention so long as the ability of siNA to 20 promote RNAi in cells is not significantly inhibited.

While chemical modification of oligonucleotide internucleotide linkages with phosphorothioate, phosphorodithioate, and/or 5'-methylphosphonate linkages improves stability, excessive modifications can cause some toxicity or decreased activity. Therefore, when designing nucleic acid molecules, the amount of these internucleotide 25 linkages should be minimized. The reduction in the concentration of these linkages should lower toxicity, resulting in increased efficacy and higher specificity of these molecules.

Short interfering nucleic acid (siNA) molecules having chemical modifications that maintain or enhance activity are provided. Such a nucleic acid is also generally more 30 resistant to nucleases than an unmodified nucleic acid. Accordingly, the *in vitro* and/or *in vivo* activity should not be significantly lowered. In cases in which modulation is the

goal, therapeutic nucleic acid molecules delivered exogenously should optimally be stable within cells until translation of the target RNA has been modulated long enough to reduce the levels of the undesirable protein. This period of time varies between hours to days depending upon the disease state. Improvements in the chemical synthesis of RNA and DNA (Wincott *et al.*, 1995, *Nucleic Acids Res.* 23, 2677; Caruthers *et al.*, 1992, *Methods in Enzymology* 211, 3-19 (incorporated by reference herein)) have expanded the ability to modify nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability, as described above.

In one embodiment, nucleic acid molecules of the invention include one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) G-clamp nucleotides. A G-clamp nucleotide is a modified cytosine analog wherein the modifications confer the ability to hydrogen bond both Watson-Crick and Hoogsteen faces of a complementary guanine within a duplex, see for example Lin and Matteucci, 1998, *J. Am. Chem. Soc.*, 120, 8531-8532. A single G-clamp analog substitution within an oligonucleotide can result in substantially enhanced helical thermal stability and mismatch discrimination when hybridized to complementary oligonucleotides. The inclusion of such nucleotides in nucleic acid molecules of the invention results in both enhanced affinity and specificity to nucleic acid targets, complementary sequences, or template strands. In another embodiment, nucleic acid molecules of the invention include one or more (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) LNA "locked nucleic acid" nucleotides such as a 2', 4'-C methylene bicyclo nucleotide (see for example Wengel *et al.*, International PCT Publication No. WO 00/66604 and WO 99/14226).

In another embodiment, the invention features conjugates and/or complexes of siNA molecules of the invention. Such conjugates and/or complexes can be used to facilitate delivery of siNA molecules into a biological system, such as a cell. The conjugates and complexes provided by the instant invention can impart therapeutic activity by transferring therapeutic compounds across cellular membranes, altering the pharmacokinetics, and/or modulating the localization of nucleic acid molecules of the invention. The present invention encompasses the design and synthesis of novel conjugates and complexes for the delivery of molecules, including, but not limited to, small molecules, lipids, cholesterol, phospholipids, nucleosides, nucleotides, nucleic

acids, antibodies, toxins, negatively charged polymers and other polymers, for example proteins, peptides, hormones, carbohydrates, polyethylene glycols, or polyamines, across cellular membranes. In general, the transporters described are designed to be used either individually or as part of a multi-component system, with or without degradable linkers.

- 5 These compounds are expected to improve delivery and/or localization of nucleic acid molecules of the invention into a number of cell types originating from different tissues, in the presence or absence of serum (see Sullenger and Cech, U.S. Pat. No. 5,854,038). Conjugates of the molecules described herein can be attached to biologically active molecules via linkers that are biodegradable, such as biodegradable nucleic acid linker
10 molecules.

The term "biodegradable linker" as used herein, refers to a nucleic acid or non-nucleic acid linker molecule that is designed as a biodegradable linker to connect one molecule to another molecule, for example, a biologically active molecule to a siNA molecule of the invention or the sense and antisense strands of a siNA molecule of the
15 invention. The biodegradable linker is designed such that its stability can be modulated for a particular purpose, such as delivery to a particular tissue or cell type. The stability of a nucleic acid-based biodegradable linker molecule can be modulated by using various chemistries, for example combinations of ribonucleotides, deoxyribonucleotides, and chemically-modified nucleotides, such as 2'-O-methyl, 2'-fluoro, 2'-amino, 2'-O-amino,
20 2'-C-allyl, 2'-O-allyl, and other 2'-modified or base modified nucleotides. The biodegradable nucleic acid linker molecule can be a dimer, trimer, tetramer or longer nucleic acid molecule, for example, an oligonucleotide of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 nucleotides in length, or can comprise a single nucleotide with a phosphorus-based linkage, for example, a phosphoramidate or
25 phosphodiester linkage. The biodegradable nucleic acid linker molecule can also comprise nucleic acid backbone, nucleic acid sugar, or nucleic acid base modifications.

The term "biodegradable" as used herein, refers to degradation in a biological system, for example enzymatic degradation or chemical degradation.

The term "biologically active molecule" as used herein, refers to compounds or
30 molecules that are capable of eliciting or modifying a biological response in a system. Non-limiting examples of biologically active siNA molecules either alone or in

combination with other molecules contemplated by the instant invention include therapeutically active molecules such as antibodies, cholesterol, hormones, antivirals, peptides, proteins, chemotherapeutics, small molecules, vitamins, co-factors, nucleosides, nucleotides, oligonucleotides, enzymatic nucleic acids, antisense nucleic acids, triplex forming oligonucleotides, 2,5-A chimeras, siNA, dsRNA, allozymes, aptamers, decoys and analogs thereof. Biologically active molecules of the invention also include molecules capable of modulating the pharmacokinetics and/or pharmacodynamics of other biologically active molecules, for example, lipids and polymers such as polyamines, polyamides, polyethylene glycol and other polyethers.

10 The term "phospholipid" as used herein, refers to a hydrophobic molecule comprising at least one phosphorus group. For example, a phospholipid can comprise a phosphorus-containing group and saturated or unsaturated alkyl group, optionally substituted with OH, COOH, oxo, amine, or substituted or unsubstituted aryl groups.

15 Therapeutic nucleic acid molecules (*e.g.*, siNA molecules) delivered exogenously optimally are stable within cells until reverse transcription of the RNA has been modulated long enough to reduce the levels of the RNA transcript. The nucleic acid molecules are resistant to nucleases in order to function as effective intracellular therapeutic agents. Improvements in the chemical synthesis of nucleic acid molecules described in the instant invention and in the art have expanded the ability to modify
20 nucleic acid molecules by introducing nucleotide modifications to enhance their nuclease stability as described above.

25 In yet another embodiment, siNA molecules having chemical modifications that maintain or enhance enzymatic activity of proteins involved in RNAi are provided. Such nucleic acids are also generally more resistant to nucleases than unmodified nucleic acids. Thus, *in vitro* and/or *in vivo* the activity should not be significantly lowered.

30 Use of the nucleic acid-based molecules of the invention will lead to better treatment of the disease progression by affording the possibility of combination therapies (*e.g.*, multiple siNA molecules targeted to different genes; nucleic acid molecules coupled with known small molecule modulators; or intermittent treatment with combinations of molecules, including different motifs and/or other chemical or

biological molecules). The treatment of subjects with siNA molecules can also include combinations of different types of nucleic acid molecules, such as enzymatic nucleic acid molecules (ribozymes), allozymes, antisense, 2,5-A oligoadenylate, decoys, and aptamers.

5 In another aspect a siNA molecule of the invention comprises one or more 5' and/or a 3'-cap structure, for example on only the sense siNA strand, the antisense siNA strand, or both siNA strands.

By "cap structure" is meant chemical modifications, which have been incorporated at either terminus of the oligonucleotide (see, for example, Adamic *et al.*, U.S. Pat. No. 10 5,998,203, incorporated by reference herein). These terminal modifications protect the nucleic acid molecule from exonuclease degradation, and may help in delivery and/or localization within a cell. The cap may be present at the 5'-terminus (5'-cap) or at the 3'-terminal (3'-cap) or may be present on both termini. In non-limiting examples, the 5'-cap includes, but is not limited to, glyceryl, inverted deoxy abasic residue (moiety); 4',5'- 15 methylene nucleotide; 1-(beta-D-erythrofuransyl) nucleotide, 4'-thio nucleotide; carbocyclic nucleotide; 1,5-anhydrohexitol nucleotide; L-nucleotides; alpha-nucleotides; modified base nucleotide; phosphorodithioate linkage; *threo*-pentofuransyl nucleotide; acyclic 3',4'-seco nucleotide; acyclic 3,4-dihydroxybutyl nucleotide; acyclic 3,5-dihydroxypentyl nucleotide, 3'-3'-inverted nucleotide moiety; 3'-3'-inverted abasic 20 moiety; 3'-2'-inverted nucleotide moiety; 3'-2'-inverted abasic moiety; 1,4-butanediol phosphate; 3'-phosphoramidate; hexylphosphate; aminohexyl phosphate; 3'-phosphate; 3'-phosphorothioate; phosphorodithioate; or bridging or non-bridging methylphosphonate moiety.

Non-limiting examples of the 3'-cap include, but are not limited to, glyceryl, 25 inverted deoxy abasic residue (moiety), 4', 5'-methylene nucleotide; 1-(beta-D-erythrofuransyl) nucleotide; 4'-thio nucleotide, carbocyclic nucleotide; 5'-amino-alkyl phosphate; 1,3-diamino-2-propyl phosphate; 3-aminopropyl phosphate; 6-aminoethyl phosphate; 1,2-aminododecyl phosphate; hydroxypropyl phosphate; 1,5-anhydrohexitol nucleotide; L-nucleotide; alpha-nucleotide; modified base nucleotide; 30 phosphorodithioate; *threo*-pentofuransyl nucleotide; acyclic 3',4'-seco nucleotide; 3,4-dihydroxybutyl nucleotide; 3,5-dihydroxypentyl nucleotide, 5'-5'-inverted nucleotide

moiety; 5'-5'-inverted abasic moiety; 5'-phosphoramidate; 5'-phosphorothioate; 1,4-butanediol phosphate; 5'-amino; bridging and/or non-bridging 5'-phosphoramidate, phosphorothioate and/or phosphorodithioate, bridging or non bridging methylphosphonate and 5'-mercapto moieties (for more details see Beaucage and Iyer, 5 1993, *Tetrahedron* 49, 1925; incorporated by reference herein).

By the term "non-nucleotide" is meant any group or compound which can be incorporated into a nucleic acid chain in the place of one or more nucleotide units, including either sugar and/or phosphate substitutions, and allows the remaining bases to exhibit their enzymatic activity. The group or compound is abasic in that it does not 10 contain a commonly recognized nucleotide base, such as adenosine, guanine, cytosine, uracil or thymine and therefore lacks a base at the 1'-position.

An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain, branched-chain, and cyclic alkyl groups. Preferably, the alkyl group has 1 to 12 carbons. More preferably, it is a lower alkyl of from 1 to 7 carbons, more preferably 1 to 15 4 carbons. The alkyl group can be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO₂ or N(CH₃)₂, amino, or SH. The term also includes alkenyl groups that are unsaturated hydrocarbon groups containing at least one carbon-carbon double bond, including straight-chain, branched-chain, and cyclic groups. Preferably, the alkenyl group has 1 to 12 carbons. 20 More preferably, it is a lower alkenyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkenyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO₂, halogen, N(CH₃)₂, amino, or SH. The term "alkyl" also includes alkynyl groups that have an unsaturated hydrocarbon group containing at least one carbon-carbon triple bond, 25 including straight-chain, branched-chain, and cyclic groups. Preferably, the alkynyl group has 1 to 12 carbons. More preferably, it is a lower alkynyl of from 1 to 7 carbons, more preferably 1 to 4 carbons. The alkynyl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably, hydroxyl, cyano, alkoxy, =O, =S, NO₂ or N(CH₃)₂, amino or SH.

Such alkyl groups can also include aryl, alkylaryl, carbocyclic aryl, heterocyclic aryl, amide and ester groups. An "aryl" group refers to an aromatic group that has at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl and biaryl groups, all of which may be optionally substituted. The preferred substituent(s) of aryl groups are halogen, trihalomethyl, hydroxyl, SH, OH, cyano, alkoxy, alkyl, alkenyl, alkynyl, and amino groups. An "alkylaryl" group refers to an alkyl group (as described above) covalently joined to an aryl group (as described above). Carbocyclic aryl groups are groups wherein the ring atoms on the aromatic ring are all carbon atoms. The carbon atoms are optionally substituted. Heterocyclic aryl groups are groups having from 1 to 3 heteroatoms as ring atoms in the aromatic ring and the remainder of the ring atoms are carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen, and include furanyl, thienyl, pyridyl, pyrrolyl, N-lower alkyl pyrrolo, pyrimidyl, pyrazinyl, imidazolyl and the like, all optionally substituted. An "amide" refers to an -C(O)-NH-R, where R is either alkyl, aryl, alkylaryl or hydrogen. An "ester" refers to an -C(O)-OR', where R is either alkyl, aryl, alkylaryl or hydrogen.

By "nucleotide" as used herein is as recognized in the art to include natural bases (standard), and modified bases well known in the art. Such bases are generally located at the 1' position of a nucleotide sugar moiety. Nucleotides generally comprise a base, sugar and a phosphate group. The nucleotides can be unmodified or modified at the sugar, phosphate and/or base moiety, (also referred to interchangeably as nucleotide analogs, modified nucleotides, non-natural nucleotides, non-standard nucleotides and other; see, for example, Usman and McSwiggen, *supra*; Eckstein *et al.*, International PCT Publication No. WO 92/07065; Usman *et al.*, International PCT Publication No. WO 93/15187; Uhlman & Peyman, *supra*, all are hereby incorporated by reference herein). There are several examples of modified nucleic acid bases known in the art as summarized by Limbach *et al.*, 1994, *Nucleic Acids Res.* 22, 2183. Some of the non-limiting examples of base modifications that can be introduced into nucleic acid molecules include, inosine, purine, pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2, 4, 6-trimethoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (*e.g.*, 5-methylcytidine), 5-alkyluridines (*e.g.*, ribothymidine), 5-halouridine (*e.g.*, 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (*e.g.* 6-methyluridine), propyne, and others (Burgin *et al.*, 1996, *Biochemistry*, 35, 14090;

Uhlman & Peyman, *supra*). By "modified bases" in this aspect is meant nucleotide bases other than adenine, guanine, cytosine and uracil at 1' position or their equivalents.

In one embodiment, the invention features modified siNA molecules, with phosphate backbone modifications comprising one or more phosphorothioate, phosphorodithioate, methylphosphonate, phosphotriester, morpholino, amidate, carbamate, carboxymethyl, acetamdate, polyamide, sulfonate, sulfonamide, sulfamate, formacetal, thioformacetal, and/or alkylsilyl, substitutions. For a review of oligonucleotide backbone modifications, see Hunziker and Leumann, 1995, *Nucleic Acid Analogues: Synthesis and Properties*, in *Modern Synthetic Methods*, VCH, 331-417, and Mesmaeker *et al.*, 1994, *Novel Backbone Replacements for Oligonucleotides*, in *Carbohydrate Modifications in Antisense Research*, ACS, 24-39.

By "abasic" is meant sugar moieties lacking a base or having other chemical groups in place of a base at the 1' position, see for example Adamic *et al.*, U.S. Pat. No. 5,998,203.

By "unmodified nucleoside" is meant one of the bases adenine, cytosine, guanine, thymine, or uracil joined to the 1' carbon of β -D-ribo-furanose.

By "modified nucleoside" is meant any nucleotide base which contains a modification in the chemical structure of an unmodified nucleotide base, sugar and/or phosphate. Non-limiting examples of modified nucleotides are shown by Formulae I-VII and/or other modifications described herein.

In connection with 2'-modified nucleotides as described for the present invention, by "amino" is meant 2'-NH₂ or 2'-O- NH₂, which can be modified or unmodified. Such modified groups are described, for example, in Eckstein *et al.*, U.S. Pat. No. 5,672,695 and Matulic-Adamic *et al.*, U.S. Pat. No. 6,248,878, which are both incorporated by reference in their entireties.

Various modifications to nucleic acid siNA structure can be made to enhance the utility of these molecules. Such modifications will enhance shelf-life, half-life *in vitro*, stability, and ease of introduction of such oligonucleotides to the target site, *e.g.*, to

enhance penetration of cellular membranes, and confer the ability to recognize and bind to targeted cells.

Administration of Nucleic Acid Molecules

A siRNA molecule of the invention can be adapted for use to treat for example SARS virus infection, acute respiratory failure, viral pneumonia, and other indications that can respond to the level of SARS in a cell or tissue, alone or in combination with other therapies. For example, a siNA molecule can comprise a delivery vehicle, including liposomes, for administration to a subject, carriers and diluents and their salts, and/or can be present in pharmaceutically acceptable formulations. Methods for the delivery of nucleic acid molecules are described in Akhtar *et al.*, 1992, *Trends Cell Bio.*, 2, 139; *Delivery Strategies for Antisense Oligonucleotide Therapeutics*, ed. Akhtar, 1995, Maurer *et al.*, 1999, *Mol. Membr. Biol.*, 16, 129-140; Hofland and Huang, 1999, *Handb. Exp. Pharmacol.*, 137, 165-192; and Lee *et al.*, 2000, *ACS Symp. Ser.*, 752, 184-192, all of which are incorporated herein by reference. Beigelman *et al.*, U.S. Pat. No. 6,395,713 and Sullivan *et al.*, PCT WO 94/02595 further describe the general methods for delivery of nucleic acid molecules. These protocols can be utilized for the delivery of virtually any nucleic acid molecule. Nucleic acid molecules can be administered to cells by a variety of methods known to those of skill in the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as biodegradable polymers, hydrogels, cyclodextrins (see for example Gonzalez *et al.*, 1999, *Bioconjugate Chem.*, 10, 1068-1074; Wang *et al.*, International PCT publication Nos. WO 03/47518 and WO 03/46185), poly(lactic-co-glycolic)acid (PLGA) and PLCA microspheres (see for example US Patent 6,447,796 and US Patent Application Publication No. US 2002130430), biodegradable nanocapsules, and bioadhesive microspheres, or by proteinaceous vectors (O'Hare and Normand, International PCT Publication No. WO 00/53722). In another embodiment, the nucleic acid molecules of the invention can also be formulated or complexed with polyethyleneimine and derivatives thereof, such as polyethyleneimine-polyethyleneglycol-N-acetylgalactosamine (PEI-PEG-GAL) or polyethyleneimine-polyethyleneglycol-tri-N-acetylgalactosamine (PEI-PEG-triGAL) derivatives.

Alternatively, the nucleic acid/vehicle combination is locally delivered by direct injection or by use of an infusion pump.

In one embodiment, the nucleic acid molecules or the invention are administered via pulmonary delivery, such as by inhalation of an aerosol or spray dried formulation administered by an inhalation device or nebulizer, providing rapid local uptake of the nucleic acid molecules into relevant pulmonary tissues. Solid particulate compositions containing respirable dry particles of micronized nucleic acid compositions can be prepared by grinding dried or lyophilized nucleic acid compositions, and then passing the micronized composition through, for example, a 400 mesh screen to break up or separate out large agglomerates. A solid particulate composition comprising the nucleic acid compositions of the invention can optionally contain a dispersant which serves to facilitate the formation of an aerosol as well as other therapeutic compounds. A suitable dispersant is lactose, which can be blended with the nucleic acid compound in any suitable ratio, such as a 1 to 1 ratio by weight.

Aerosols of liquid particles comprising a nucleic acid composition of the invention can be produced by any suitable means, such as with a nebulizer (see for example US 4,501,729). Nebulizers are commercially available devices which transform solutions or suspensions of an active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebulizers comprise the active ingredient in a liquid carrier in an amount of up to 40% w/w preferably less than 20% w/w of the formulation. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride or other suitable salts. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxybenzoate, anti-oxidants, flavorings, volatile oils, buffering agents and emulsifiers and other formulation surfactants. The aerosols of solid particles comprising the active composition and surfactant can likewise be produced with any solid particulate aerosol generator. Aerosol generators for administering solid particulate therapeutics to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a therapeutic composition at a rate

suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which can be delivered by means of an insufflator. In the insufflator, the powder, e.g., a metered dose thereof effective to carry out the
5 treatments described herein, is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as
10 lactose, and an optional surfactant. The active ingredient typically comprises from 0.1 to 100 w/w of the formulation. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquified propellant. During use these devices discharge the formulation through a valve adapted
15 to deliver a metered volume to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation can additionally contain one or more co-solvents, for example, ethanol, emulsifiers and other formulation surfactants, such as oleic acid or
20 sorbitan trioleate, anti-oxidants and suitable flavoring agents. Other methods for pulmonary delivery are described in, for example US Patent Application No. 20040037780, and US Patent Nos. 6,592,904; 6,582,728; 6,565,885.

In one embodiment, a siNA molecule of the invention is complexed with membrane disruptive agents such as those described in U.S. Patent Application
25 Publication No. 20010007666, incorporated by reference herein in its entirety including the drawings. In another embodiment, the membrane disruptive agent or agents and the siNA molecule are also complexed with a cationic lipid or helper lipid molecule, such as those lipids described in U.S. Patent No. 6,235,310, incorporated by reference herein in its entirety including the drawings.

30 Thus, the invention features a pharmaceutical composition comprising one or more nucleic acid(s) of the invention in an acceptable carrier, such as a stabilizer, buffer, and

the like. The polynucleotides of the invention can be administered (*e.g.*, RNA, DNA or protein) and introduced into a subject by any standard means, with or without stabilizers, buffers, and the like, to form a pharmaceutical composition. When it is desired to use a liposome delivery mechanism, standard protocols for formation of liposomes can be followed. The compositions of the present invention can also be formulated and used as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions, suspensions for injectable administration, and the other compositions known in the art.

The present invention also includes pharmaceutically acceptable formulations of the compounds described. These formulations include salts of the above compounds, *e.g.*, acid addition salts, for example, salts of hydrochloric, hydrobromic, acetic acid, and benzene sulfonic acid.

A pharmacological composition or formulation refers to a composition or formulation in a form suitable for administration, *e.g.*, systemic administration, into a cell or subject, including for example a human. Suitable forms, in part, depend upon the use or the route of entry, for example oral, transdermal, or by injection. Such forms should not prevent the composition or formulation from reaching a target cell (*i.e.*, a cell to which the negatively charged nucleic acid is desirable for delivery). For example, pharmacological compositions injected into the blood stream should be soluble. Other factors are known in the art, and include considerations such as toxicity and forms that prevent the composition or formulation from exerting its effect.

By "systemic administration" is meant *in vivo* systemic absorption or accumulation of drugs in the blood stream followed by distribution throughout the entire body. Administration routes that lead to systemic absorption include, without limitation: intravenous, subcutaneous, intraperitoneal, inhalation, oral, intrapulmonary and intramuscular. Each of these administration routes exposes the siNA molecules of the invention to an accessible diseased tissue. The rate of entry of a drug into the circulation has been shown to be a function of molecular weight or size. The use of a liposome or other drug carrier comprising the compounds of the instant invention can potentially localize the drug, for example, in certain tissue types, such as the tissues of the reticular endothelial system (RES). A liposome formulation that can facilitate the

association of drug with the surface of cells, such as, lymphocytes and macrophages is also useful. This approach can provide enhanced delivery of the drug to target cells by taking advantage of the specificity of macrophage and lymphocyte immune recognition of abnormal cells, such as cells producing excess repeat expansion genes.

5 By "pharmaceutically acceptable formulation" is meant, a composition or formulation that allows for the effective distribution of the nucleic acid molecules of the instant invention in the physical location most suitable for their desired activity. Non-limiting examples of agents suitable for formulation with the nucleic acid molecules of the instant invention include: P-glycoprotein inhibitors (such as Pluronic P85);,
10 biodegradable polymers, such as poly (DL-lactide-coglycolide) microspheres for sustained release delivery (Emerich, DF *et al.*, 1999, *Cell Transplant*, 8, 47-58); and loaded nanoparticles, such as those made of polybutylcyanoacrylate. Other non-limiting examples of delivery strategies for the nucleic acid molecules of the instant invention include material described in Boado *et al.*, 1998, *J. Pharm. Sci.*, 87, 1308-1315; Tyler *et al.*, 1999, *FEBS Lett.*, 421, 280-284; Pardridge *et al.*, 1995, *PNAS USA.*, 92, 5592-5596;
15 Boado, 1995, *Adv. Drug Delivery Rev.*, 15, 73-107; Aldrian-Herrada *et al.*, 1998, *Nucleic Acids Res.*, 26, 4910-4916; and Tyler *et al.*, 1999, *PNAS USA.*, 96, 7053-7058.

The invention also features the use of the composition comprising surface-modified liposomes containing poly (ethylene glycol) lipids (PEG-modified, or long-circulating liposomes or stealth liposomes). These formulations offer a method for
20 increasing the accumulation of drugs in target tissues. This class of drug carriers resists opsonization and elimination by the mononuclear phagocytic system (MPS or RES), thereby enabling longer blood circulation times and enhanced tissue exposure for the encapsulated drug (Lasic *et al.* *Chem. Rev.* 1995, 95, 2601-2627; Ishiwata *et al.*, *Chem. Pharm. Bull.* 1995, 43, 1005-1011). Such liposomes have been shown to accumulate selectively in tumors, presumably by extravasation and capture in the neovascularized target tissues (Lasic *et al.*, *Science* 1995, 267, 1275-1276; Oku *et al.*, 1995, *Biochim. Biophys. Acta*, 1238, 86-90). The long-circulating liposomes enhance the pharmacokinetics and pharmacodynamics of DNA and RNA, particularly compared to
30 conventional cationic liposomes which are known to accumulate in tissues of the MPS (Liu *et al.*, *J. Biol. Chem.* 1995, 270, 24864-24870; Choi *et al.*, International PCT

Publication No. WO 96/10391; Ansell *et al.*, International PCT Publication No. WO 96/10390; Holland *et al.*, International PCT Publication No. WO 96/10392). Long-circulating liposomes are also likely to protect drugs from nuclease degradation to a greater extent compared to cationic liposomes, based on their ability to avoid
5 accumulation in metabolically aggressive MPS tissues such as the liver and spleen.

The present invention also includes compositions prepared for storage or administration that include a pharmaceutically effective amount of the desired compounds in a pharmaceutically acceptable carrier or diluent. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described,
10 for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co. (A.R. Gennaro edit. 1985), hereby incorporated by reference herein. For example, preservatives, stabilizers, dyes and flavoring agents can be provided. These include sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid. In addition, antioxidants and suspending agents can be used.

15 A pharmaceutically effective dose is that dose required to prevent, inhibit the occurrence, or treat (alleviate a symptom to some extent, preferably all of the symptoms) of a disease state. The pharmaceutically effective dose depends on the type of disease, the composition used, the route of administration, the type of mammal being treated, the physical characteristics of the specific mammal under consideration, concurrent
20 medication, and other factors that those skilled in the medical arts will recognize. Generally, an amount between 0.1 mg/kg and 100 mg/kg body weight/day of active ingredients is administered dependent upon potency of the negatively charged polymer.

The nucleic acid molecules of the invention and formulations thereof can be administered orally, topically, parenterally, by inhalation or spray, or rectally in dosage
25 unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and/or vehicles. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (*e.g.*, intravenous), intramuscular, or intrathecal injection or infusion techniques and the like. In addition, there is provided a pharmaceutical formulation comprising a nucleic acid molecule of the invention and a
30 pharmaceutically acceptable carrier. One or more nucleic acid molecules of the invention can be present in association with one or more non-toxic pharmaceutically

acceptable carriers and/or diluents and/or adjuvants, and if desired other active ingredients. The pharmaceutical compositions containing nucleic acid molecules of the invention can be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard
5 or soft capsules, or syrups or elixirs.

Compositions intended for oral use can be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more such sweetening agents, flavoring agents, coloring agents or preservative agents in order to provide pharmaceutically elegant and palatable
10 preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be, for example, inert diluents; such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for
15 example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl
20 monostearate or glyceryl distearate can be employed.

Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

25 Aqueous suspensions contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents can be a naturally-occurring phosphatide, for example,
30 lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain

aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions can also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions can contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents can be added to provide palatable oral preparations. These compositions can be preserved by the addition of an anti-oxidant such as ascorbic acid

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

Pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a

demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above.

5 The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any

10 bland fixed oil can be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The nucleic acid molecules of the invention can also be administered in the form of suppositories, *e.g.*, for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at

15 ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

Nucleic acid molecules of the invention can be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either

20 be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per subject per day). The amount of active ingredient that can be

25 combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Dosage unit forms generally contain between from about 1 mg to about 500 mg of an active ingredient.

It is understood that the specific dose level for any particular subject depends upon a variety of factors including the activity of the specific compound employed, the age,

30 body weight, general health, sex, diet, time of administration, route of administration,

and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition can also be added to the animal feed or drinking water. It can be convenient to formulate the animal feed and drinking water compositions so that the animal takes in a therapeutically appropriate quantity of the composition along with its diet. It can also be convenient to present the composition as a premix for addition to the feed or drinking water.

The nucleic acid molecules of the present invention can also be administered to a subject in combination with other therapeutic compounds to increase the overall therapeutic effect. The use of multiple compounds to treat an indication can increase the beneficial effects while reducing the presence of side effects.

In one embodiment, the invention comprises compositions suitable for administering nucleic acid molecules of the invention to specific cell types. For example, the asialoglycoprotein receptor (ASGPr) (Wu and Wu, 1987, *J. Biol. Chem.* 262, 4429-4432) is unique to hepatocytes and binds branched galactose-terminal glycoproteins, such as asialoorosomucoid (ASOR). In another example, the folate receptor is overexpressed in many cancer cells. Binding of such glycoproteins, synthetic glycoconjugates, or folates to the receptor takes place with an affinity that strongly depends on the degree of branching of the oligosaccharide chain, for example, triantennary structures are bound with greater affinity than biantennary or monoantennary chains (Baenziger and Fiete, 1980, *Cell*, 22, 611-620; Connolly *et al.*, 1982, *J. Biol. Chem.*, 257, 939-945). Lee and Lee, 1987, *Glycoconjugate J.*, 4, 317-328, obtained this high specificity through the use of N-acetyl-D-galactosamine as the carbohydrate moiety, which has higher affinity for the receptor, compared to galactose. This "clustering effect" has also been described for the binding and uptake of mannosyl-terminating glycoproteins or glycoconjugates (Ponpipom *et al.*, 1981, *J. Med. Chem.*, 24, 1388-1395). The use of galactose, galactosamine, or folate based conjugates to transport exogenous compounds across cell membranes can provide a targeted delivery approach to, for example, the treatment of liver disease, cancers of the liver, or other cancers. The use of bioconjugates can also provide a reduction in the required dose of therapeutic compounds required for treatment. Furthermore, therapeutic bioavailability,

pharmacodynamics, and pharmacokinetic parameters can be modulated through the use of nucleic acid bioconjugates of the invention. Non-limiting examples of such bioconjugates are described in Vargeese *et al.*, USSN 10/201,394, filed August 13, 2001; and Matulic-Adamic *et al.*, USSN 10/151,116, filed May 17, 2002. In one embodiment, 5 nucleic acid molecules of the invention are complexed with or covalently attached to nanoparticles, such as Hepatitis B virus S, M, or L envelope proteins (see for example Yamado *et al.*, 2003, *Nature Biotechnology*, 21, 885). In one embodiment, nucleic acid molecules of the invention are delivered with specificity for human tumor cells, specifically non-apoptotic human tumor cells including for example T-cells, hepatocytes, 10 breast carcinoma cells, ovarian carcinoma cells, melanoma cells, intestinal epithelial cells, prostate cells, testicular cells, non-small cell lung cancers, small cell lung cancers, etc.

Alternatively, certain siNA molecules of the instant invention can be expressed within cells from eukaryotic promoters (*e.g.*, Izant and Weintraub, 1985, *Science*, 229, 345; McGarry and Lindquist, 1986, *Proc. Natl. Acad. Sci.*, USA 83, 399; Scanlon *et al.*, 15 1991, *Proc. Natl. Acad. Sci. USA*, 88, 10591-5; Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Dropulic *et al.*, 1992, *J. Virol.*, 66, 1432-41; Weerasinghe *et al.*, 1991, *J. Virol.*, 65, 5531-4; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. USA*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Sarver *et al.*, 1990 *Science*, 247, 20 1222-1225; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Good *et al.*, 1997, *Gene Therapy*, 4, 45. Those skilled in the art realize that any nucleic acid can be expressed in eukaryotic cells from the appropriate DNA/RNA vector. The activity of such nucleic acids can be augmented by their release from the primary transcript by a enzymatic nucleic acid (Draper *et al.*, PCT WO 93/23569, and Sullivan *et al.*, PCT WO 25 94/02595; Ohkawa *et al.*, 1992, *Nucleic Acids Symp. Ser.*, 27, 15-6; Taira *et al.*, 1991, *Nucleic Acids Res.*, 19, 5125-30; Ventura *et al.*, 1993, *Nucleic Acids Res.*, 21, 3249-55; Chowrira *et al.*, 1994, *J. Biol. Chem.*, 269, 25856.

In another aspect of the invention, RNA molecules of the present invention can be expressed from transcription units (see for example Couture *et al.*, 1996, *TIG.*, 12, 510) 30 inserted into DNA or RNA vectors. The recombinant vectors can be DNA plasmids or viral vectors. siNA expressing viral vectors can be constructed based on, but not limited

to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. In another embodiment, pol III based constructs are used to express nucleic acid molecules of the invention (see for example Thompson, U.S. Pats. Nos. 5,902,880 and 6,146,886). The recombinant vectors capable of expressing the siNA molecules can be delivered as described above, and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression of nucleic acid molecules. Such vectors can be repeatedly administered as necessary. Once expressed, the siNA molecule interacts with the target mRNA and generates an RNAi response. Delivery of siNA molecule expressing vectors can be systemic, such as by intravenous or intra-muscular administration, by administration to target cells ex-planted from a subject followed by reintroduction into the subject, or by any other means that would allow for introduction into the desired target cell (for a review see Couture *et al.*, 1996, *TIG.*, 12, 510).

In one aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one siNA molecule of the instant invention. The expression vector can encode one or both strands of a siNA duplex, or a single self-complementary strand that self hybridizes into a siNA duplex. The nucleic acid sequences encoding the siNA molecules of the instant invention can be operably linked in a manner that allows expression of the siNA molecule (see for example Paul *et al.*, 2002, *Nature Biotechnology*, 19, 505; Miyagishi and Taira, 2002, *Nature Biotechnology*, 19, 497; Lee *et al.*, 2002, *Nature Biotechnology*, 19, 500; and Novina *et al.*, 2002, *Nature Medicine*, advance online publication doi:10.1038/nm725).

In another aspect, the invention features an expression vector comprising: a) a transcription initiation region (*e.g.*, eukaryotic pol I, II or III initiation region); b) a transcription termination region (*e.g.*, eukaryotic pol I, II or III termination region); and c) a nucleic acid sequence encoding at least one of the siNA molecules of the instant invention, wherein said sequence is operably linked to said initiation region and said termination region in a manner that allows expression and/or delivery of the siNA molecule. The vector can optionally include an open reading frame (ORF) for a protein operably linked on the 5' side or the 3'-side of the sequence encoding the siNA of the invention; and/or an intron (intervening sequences).

Transcription of the siNA molecule sequences can be driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters are expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type depends on the nature of the gene regulatory sequences (enhancers, silencers, etc.) present nearby. Prokaryotic RNA polymerase promoters are also used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells (Elroy-Stein and Moss, 1990, *Proc. Natl. Acad. Sci. U S A*, 87, 6743-7; Gao and Huang 1993, *Nucleic Acids Res.*, 21, 2867-72; Lieber *et al.*, 1993, *Methods Enzymol.*, 217, 47-66; Zhou *et al.*, 1990, *Mol. Cell. Biol.*, 10, 4529-37). Several investigators have demonstrated that nucleic acid molecules expressed from such promoters can function in mammalian cells (e.g. Kashani-Sabet *et al.*, 1992, *Antisense Res. Dev.*, 2, 3-15; Ojwang *et al.*, 1992, *Proc. Natl. Acad. Sci. U S A*, 89, 10802-6; Chen *et al.*, 1992, *Nucleic Acids Res.*, 20, 4581-9; Yu *et al.*, 1993, *Proc. Natl. Acad. Sci. U S A*, 90, 6340-4; L'Huillier *et al.*, 1992, *EMBO J.*, 11, 4411-8; Lisiewicz *et al.*, 1993, *Proc. Natl. Acad. Sci. U. S. A*, 90, 8000-4; Thompson *et al.*, 1995, *Nucleic Acids Res.*, 23, 2259; Sullenger & Cech, 1993, *Science*, 262, 1566). More specifically, transcription units such as the ones derived from genes encoding U6 small nuclear (snRNA), transfer RNA (tRNA) and adenovirus VA RNA are useful in generating high concentrations of desired RNA molecules such as siNA in cells (Thompson *et al.*, *supra*; Couture and Stinchcomb, 1996, *supra*; Noonberg *et al.*, 1994, *Nucleic Acid Res.*, 22, 2830; Noonberg *et al.*, U.S. Pat. No. 5,624,803; Good *et al.*, 1997, *Gene Ther.*, 4, 45; Beigelman *et al.*, International PCT Publication No. WO 96/18736. The above siNA transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated virus vectors), or viral RNA vectors (such as retroviral or alphavirus vectors) (for a review see Couture and Stinchcomb, 1996, *supra*).

In another aspect the invention features an expression vector comprising a nucleic acid sequence encoding at least one of the siNA molecules of the invention in a manner that allows expression of that siNA molecule. The expression vector comprises in one embodiment; a) a transcription initiation region; b) a transcription termination region; and c) a nucleic acid sequence encoding at least one strand of the siNA molecule,

wherein the sequence is operably linked to the initiation region and the termination region in a manner that allows expression and/or delivery of the siNA molecule.

In another embodiment the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an open reading frame; and d) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the open reading frame and the termination region in a manner that allows expression and/or delivery of the siNA molecule. In yet another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; and d) a nucleic acid sequence encoding at least one siNA molecule, wherein the sequence is operably linked to the initiation region, the intron and the termination region in a manner which allows expression and/or delivery of the nucleic acid molecule.

In another embodiment, the expression vector comprises: a) a transcription initiation region; b) a transcription termination region; c) an intron; d) an open reading frame; and e) a nucleic acid sequence encoding at least one strand of a siNA molecule, wherein the sequence is operably linked to the 3'-end of the open reading frame and wherein the sequence is operably linked to the initiation region, the intron, the open reading frame and the termination region in a manner which allows expression and/or delivery of the siNA molecule.

SARS virus biology and biochemistry

The following discussion is adapted from the report, "Preliminary Clinical Description of Severe Acute Respiratory Syndrome", World Health Organization, Geneva, Switzerland, available at the Centers for Disease Control and Prevention website.

Severe acute respiratory syndrome (SARS) is a viral respiratory illness caused by a coronavirus, called SARS-associated coronavirus (SARS-CoV). SARS was first reported in Asia in February 2003. Over the next few months, the illness spread to more than two dozen countries in North America, South America, Europe, and Asia before the SARS

global outbreak of 2003 was contained. According to the World Health Organization (WHO), a total of 8,098 people worldwide became sick with SARS during the 2003 outbreak. Of these, 774 died.

5 The incubation period for SARS is typically 2--7 days; however, isolated reports have suggested an incubation period as long as 10 days. The illness begins generally with a prodrome of fever ($>100.4^{\circ}\text{F}$ [$>38.0^{\circ}\text{C}$]). Fever often is high, sometimes is associated with chills and rigors, and might be accompanied by other symptoms, including headache, malaise, and myalgia. At the onset of illness, some persons have mild respiratory symptoms. Typically, rash and neurologic or gastrointestinal findings are
10 absent; however, some patients have reported diarrhea during the febrile prodrome.

After 3--7 days, a lower respiratory phase begins with the onset of a dry, nonproductive cough or dyspnea, which might be accompanied by or progress to hypoxemia. In 10%--20% of cases, the respiratory illness is severe enough to require intubation and mechanical ventilation. Death may result from progressive respiratory
15 failure due to alveolar damage. The case-fatality rate among persons with illness meeting the current WHO case definition of SARS is approximately 3%.

Chest radiographs might be normal during the febrile prodrome and throughout the course of illness. However, in a substantial proportion of patients, the respiratory phase is characterized by early focal interstitial infiltrates progressing to more generalized,
20 patchy, interstitial infiltrates. Some chest radiographs from patients in the late stages of SARS also have shown areas of consolidation.

Early in the course of disease, the absolute lymphocyte count is often decreased. Overall white blood cell counts have generally been normal or decreased. At the peak of the respiratory illness, approximately 50% of patients have leukopenia and
25 thrombocytopenia or low-normal platelet counts (50,000--150,000/ μL). Early in the respiratory phase, elevated creatine phosphokinase levels (as high as 3,000 IU/L) and hepatic transaminases (two to six times the upper limits of normal) have been noted. In the majority of patients, renal function has remained normal.

The severity of illness might be highly variable, ranging from mild illness to death. Although a few close contacts of patients with SARS have developed a similar illness, the majority have remained well. Some close contacts have reported a mild, febrile illness without respiratory signs or symptoms, suggesting the illness might not always
5 progress to the respiratory phase.

Treatment regimens have included several antibiotics to presumptively treat known bacterial agents of atypical pneumonia. In several locations, therapy also has included antiviral agents such as oseltamivir or ribavirin. Steroids have also been administered orally or intravenously to patients in combination with ribavirin and other antimicrobials.
10 At present, the most efficacious treatment regimen, if any, is unknown.

The causative agent of SARS appears to be a novel coronavirus that was isolated from patients who met the case definition of SARS (see Ksiazek et al., 2003, New England Journal of Medicine, 10.1056/NEJMoa030781. Indirect fluorescent antibody tests and enzyme-linked immunosorbent assays made with the new coronavirus isolate
15 have been used to demonstrate a virus-specific serologic response. Amplification of short regions of the polymerase gene, (the most strongly conserved part of the Coronavirus genome) by reverse transcriptase polymerase chain reaction (RT-PCR) and nucleotide sequencing revealed that the SARS virus is a novel Coronavirus which has not previously been present in human populations. This conclusion is confirmed by
20 serological (antigenic) investigations. The sequence of the SARS associated coronavirus was recently made available through the CDC.

Viral entry into cells occurs via endocytosis and membrane fusion. Replication occurs in the cytoplasm. Initially, the 5' 20kb of the (+)sense genome is translated to produce a viral polymerase, which then produces a full-length (-)sense strand. This is
25 used as a template to produce mRNA as a nested set of transcripts, all with an identical 5' non-translated leader sequence of 72nt and coincident 3' polyadenylated ends. Each mRNA is monocistronic, the genes at the 5' end being translated from the longest mRNA. These unusual cytoplasmic structures are produced not by splicing but by the polymerase during transcription. Between each of the genes there is a repeated intergenic
30 sequence - UCUAAAC - which interacts with the transcriptase plus cellular factors to splice the leader sequence onto the start of each ORF. Viral assembly occurs by budding

into the golgi apparatus, and viral particles are transported to the surface of the cell and are subsequently released.

The SARS virus can be grown in Vero cells (a fibroblast cell line isolated in 1962 from a primate). This is a novel property for human coronaviruses which usually cannot be cultivated. In these cells, virus infection results in a cytopathic effect, and budding of Coronavirus-like particles from the endoplasmic reticulum within infected cells.

Detection of the SARS virus can be accomplished with serological testing and molecular diagnostic procedures. Serological testing for anti-Coronavirus antibodies consists of indirect fluorescent antibody testing and enzyme-linked immunosorbent assays (ELISA) which detect antibodies against the virus produced in response to infection. Molecular testing consists of reverse transcriptase-polymerase chain reaction (RT-PCR) tests specific for the RNA from the novel Coronavirus.

The use of small interfering nucleic acid molecules targeting SARS genes therefore provides a class of novel therapeutic agents that can be used in the treatment and diagnosis of SARS virus infection, acute respiratory failure, viral pneumonia, or any other disease or condition that responds to modulation of SARS genes.

Examples:

The following are non-limiting examples showing the selection, isolation, synthesis and activity of nucleic acids of the instant invention.

20 Example 1: Tandem synthesis of siNA constructs

Exemplary siNA molecules of the invention are synthesized in tandem using a cleavable linker, for example, a succinyl-based linker. Tandem synthesis as described herein is followed by a one-step purification process that provides RNAi molecules in high yield. This approach is highly amenable to siNA synthesis in support of high throughput RNAi screening, and can be readily adapted to multi-column or multi-well synthesis platforms.

After completing a tandem synthesis of a siNA oligo and its complement in which the 5'-terminal dimethoxytrityl (5'-O-DMT) group remains intact (trityl on synthesis), the

oligonucleotides are deprotected as described above. Following deprotection, the siNA sequence strands are allowed to spontaneously hybridize. This hybridization yields a duplex in which one strand has retained the 5'-O-DMT group while the complementary strand comprises a terminal 5'-hydroxyl. The newly formed duplex behaves as a single molecule during routine solid-phase extraction purification (Trityl-On purification) even though only one molecule has a dimethoxytrityl group. Because the strands form a stable duplex, this dimethoxytrityl group (or an equivalent group, such as other trityl groups or other hydrophobic moieties) is all that is required to purify the pair of oligos, for example, by using a C18 cartridge.

Standard phosphoramidite synthesis chemistry is used up to the point of introducing a tandem linker, such as an inverted deoxy abasic succinate or glyceryl succinate linker (see **Figure 1**) or an equivalent cleavable linker. A non-limiting example of linker coupling conditions that can be used includes a hindered base such as diisopropylethylamine (DIPA) and/or DMAP in the presence of an activator reagent such as Bromotripyrrolidinophosphoniumhexafluorophosphate (PyBrOP). After the linker is coupled, standard synthesis chemistry is utilized to complete synthesis of the second sequence leaving the terminal the 5'-O-DMT intact. Following synthesis, the resulting oligonucleotide is deprotected according to the procedures described herein and quenched with a suitable buffer, for example with 50mM NaOAc or 1.5M $\text{NH}_4\text{H}_2\text{CO}_3$.

Purification of the siNA duplex can be readily accomplished using solid phase extraction, for example using a Waters C18 SepPak 1g cartridge conditioned with 1 column volume (CV) of acetonitrile, 2 CV H_2O , and 2 CV 50mM NaOAc. The sample is loaded and then washed with 1 CV H_2O or 50mM NaOAc. Failure sequences are eluted with 1 CV 14% ACN (Aqueous with 50mM NaOAc and 50mM NaCl). The column is then washed, for example with 1 CV H_2O followed by on-column detritylation, for example by passing 1 CV of 1% aqueous trifluoroacetic acid (TFA) over the column, then adding a second CV of 1% aqueous TFA to the column and allowing to stand for approximately 10 minutes. The remaining TFA solution is removed and the column washed with H_2O followed by 1 CV 1M NaCl and additional H_2O . The siNA duplex product is then eluted, for example, using 1 CV 20% aqueous CAN.

Figure 2 provides an example of MALDI-TOF mass spectrometry analysis of a purified siNA construct in which each peak corresponds to the calculated mass of an individual siNA strand of the siNA duplex. The same purified siNA provides three peaks when analyzed by capillary gel electrophoresis (CGE), one peak presumably corresponding to the duplex siNA, and two peaks presumably corresponding to the separate siNA sequence strands. Ion exchange HPLC analysis of the same siNA construct only shows a single peak. Testing of the purified siNA construct using a luciferase reporter assay described below demonstrated the same RNAi activity compared to siNA constructs generated from separately synthesized oligonucleotide sequence strands.

10 Example 2: Identification of potential siNA target sites in any RNA sequence

The sequence of an RNA target of interest, such as a viral or human mRNA transcript, is screened for target sites, for example by using a computer folding algorithm. In a non-limiting example, the sequence of a gene or RNA gene transcript derived from a database, such as Genbank, is used to generate siNA targets having complementarity to the target. Such sequences can be obtained from a database, or can be determined experimentally as known in the art. Target sites that are known, for example, those target sites determined to be effective target sites based on studies with other nucleic acid molecules, for example ribozymes or antisense, or those targets known to be associated with a disease or condition such as those sites containing mutations or deletions, can be used to design siNA molecules targeting those sites. Various parameters can be used to determine which sites are the most suitable target sites within the target RNA sequence. These parameters include but are not limited to secondary or tertiary RNA structure, the nucleotide base composition of the target sequence, the degree of homology between various regions of the target sequence, or the relative position of the target sequence within the RNA transcript. Based on these determinations, any number of target sites within the RNA transcript can be chosen to screen siNA molecules for efficacy, for example by using *in vitro* RNA cleavage assays, cell culture, or animal models. In a non-limiting example, anywhere from 1 to 1000 target sites are chosen within the transcript based on the size of the siNA construct to be used. High throughput screening assays can be developed for screening siNA molecules

using methods known in the art, such as with multi-well or multi-plate assays to determine efficient reduction in target gene expression.

Example 3: Selection of siNA molecule target sites in a RNA

5 The following non-limiting steps can be used to carry out the selection of siNAs targeting a given gene sequence or transcript.

1. The target sequence is parsed *in silico* into a list of all fragments or subsequences of a particular length, for example 23 nucleotide fragments, contained within the target sequence. This step is typically carried out using a custom Perl script, but commercial sequence analysis programs such as Oligo, MacVector, or the GCG
10 Wisconsin Package can be employed as well.
2. In some instances the siNAs correspond to more than one target sequence; such would be the case for example in targeting different transcripts of the same gene, targeting different transcripts of more than one gene, or for targeting both the human
15 gene and an animal homolog. In this case, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find matching sequences in each list. The subsequences are then ranked according to the number of target sequences that contain the given subsequence; the goal is to find subsequences that are present in most or all of the target sequences. Alternately, the ranking can
20 identify subsequences that are unique to a target sequence, such as a mutant target sequence. Such an approach would enable the use of siNA to target specifically the mutant sequence and not effect the expression of the normal sequence.
3. In some instances the siNA subsequences are absent in one or more sequences while present in the desired target sequence; such would be the case if the siNA targets a gene with a paralogous family member that is to remain untargeted. As in case 2
25 above, a subsequence list of a particular length is generated for each of the targets, and then the lists are compared to find sequences that are present in the target gene but are absent in the untargeted paralog.

4. The ranked siNA subsequences can be further analyzed and ranked according to GC content. A preference can be given to sites containing 30-70% GC, with a further preference to sites containing 40-60% GC.
5. The ranked siNA subsequences can be further analyzed and ranked according to self-folding and internal hairpins. Weaker internal folds are preferred; strong hairpin structures are to be avoided.
6. The ranked siNA subsequences can be further analyzed and ranked according to whether they have runs of GGG or CCC in the sequence. GGG (or even more Gs) in either strand can make oligonucleotide synthesis problematic and can potentially interfere with RNAi activity, so it is avoided whenever better sequences are available. CCC is searched in the target strand because that will place GGG in the antisense strand.
7. The ranked siNA subsequences can be further analyzed and ranked according to whether they have the dinucleotide UU (uridine dinucleotide) on the 3'-end of the sequence, and/or AA on the 5'-end of the sequence (to yield 3' UU on the antisense sequence). These sequences allow one to design siNA molecules with terminal TT thymidine dinucleotides.
8. Four or five target sites are chosen from the ranked list of subsequences as described above. For example, in subsequences having 23 nucleotides, the right 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the upper (sense) strand of the siNA duplex, while the reverse complement of the left 21 nucleotides of each chosen 23-mer subsequence are then designed and synthesized for the lower (antisense) strand of the siNA duplex (see **Tables II and III**). If terminal TT residues are desired for the sequence (as described in paragraph 7), then the two 3' terminal nucleotides of both the sense and antisense strands are replaced by TT prior to synthesizing the oligos.
9. The siNA molecules are screened in an *in vitro*, cell culture or animal model system to identify the most active siNA molecule or the most preferred target site within the target RNA sequence.

10. Other design considerations can be used when selecting target nucleic acid sequences, see for example Reynolds *et al.*, 2004, *Nature Biotechnology Advanced Online Publication*, 1 February 2004, doi:10.1038/nbt936 and Ui-Tei *et al.*, 2004, *Nucleic Acids Research*, 32, doi:10.1093/nar/gkh247.

5 In an alternate approach, a pool of siNA constructs specific to a SARS target sequence is used to screen for target sites in cells expressing SARS RNA, such as VERO cells and/or FRhk-4 cells. The general strategy used in this approach is shown in **Figure 9**. A non-limiting example of such is a pool comprising sequences having SEQ ID NOs: 1-3392. Cells expressing SARS (e.g., VERO cells and/or FRhk-4 cells) are transfected
10 with the pool of siNA constructs and cells that demonstrate a phenotype associated with SARS inhibition are sorted. The pool of siNA constructs can be expressed from transcription cassettes inserted into appropriate vectors (see for example **Figure 7** and **Figure 8**). The siNA from cells demonstrating a positive phenotypic change (e.g., decreased proliferation, decreased SARS mRNA levels or decreased SARS protein
15 expression), are sequenced to determine the most suitable target site(s) within the target SARS RNA sequence.

Example 4: SARS targeted siNA design

siNA target sites were chosen by analyzing sequences of the SARS RNA target and optionally prioritizing the target sites on the basis of folding (structure of any given
20 sequence analyzed to determine siNA accessibility to the target), by using a library of siNA molecules as described in Example 3, or alternately by using an *in vitro* siNA system as described in Example 6 herein. siNA molecules were designed that could bind each target and are optionally individually analyzed by computer folding to assess whether the siNA molecule can interact with the target sequence. Varying the length of
25 the siNA molecules can be chosen to optimize activity. Generally, a sufficient number of complementary nucleotide bases are chosen to bind to, or otherwise interact with, the target RNA, but the degree of complementarity can be modulated to accommodate siNA duplexes or varying length or base composition. By using such methodologies, siNA molecules can be designed to target sites within any known RNA sequence, for example
30 those RNA sequences corresponding to the any gene transcript.

Chemically modified siNA constructs are designed to provide nuclease stability for systemic administration in vivo and/or improved pharmacokinetic, localization, and delivery properties while preserving the ability to mediate RNAi activity. Chemical modifications as described herein are introduced synthetically using synthetic methods described herein and those generally known in the art. The synthetic siNA constructs are then assayed for nuclease stability in serum and/or cellular/tissue extracts (e.g. liver extracts). The synthetic siNA constructs are also tested in parallel for RNAi activity using an appropriate assay, such as a luciferase reporter assay as described herein or another suitable assay that can quantify RNAi activity. Synthetic siNA constructs that possess both nuclease stability and RNAi activity can be further modified and re-evaluated in stability and activity assays. The chemical modifications of the stabilized active siNA constructs can then be applied to any siNA sequence targeting any chosen RNA and used, for example, in target screening assays to pick lead siNA compounds for therapeutic development (see for example Figure 11).

Example 5: Chemical Synthesis and Purification of siNA

siNA molecules can be designed to interact with various sites in the RNA message, for example, target sequences within the RNA sequences described herein. The sequence of one strand of the siNA molecule(s) is complementary to the target site sequences described above. The siNA molecules can be chemically synthesized using methods described herein. Inactive siNA molecules that are used as control sequences can be synthesized by scrambling the sequence of the siNA molecules such that it is not complementary to the target sequence. Generally, siNA constructs can be synthesized using solid phase oligonucleotide synthesis methods as described herein (see for example Usman *et al.*, US Patent Nos. 5,804,683; 5,831,071; 5,998,203; 6,117,657; 6,353,098; 6,362,323; 6,437,117; 6,469,158; Scaringe *et al.*, US Patent Nos. 6,111,086; 6,008,400; 6,111,086 all incorporated by reference herein in their entirety).

In a non-limiting example, RNA oligonucleotides are synthesized in a stepwise fashion using the phosphoramidite chemistry as is known in the art. Standard phosphoramidite chemistry involves the use of nucleosides comprising any of 5'-O-dimethoxytrityl, 2'-O-tert-butyldimethylsilyl, 3'-O-2-Cyanoethyl N,N-diisopropylphosphoroamidite groups, and exocyclic amine protecting groups (e.g. N6-benzoyl adenosine,

N4 acetyl cytidine, and N2-isobutryl guanosine). Alternately, 2'-O-Silyl Ethers can be used in conjunction with acid-labile 2'-O-orthoester protecting groups in the synthesis of RNA as described by Scaringe *supra*. Differing 2' chemistries can require different protecting groups, for example 2'-deoxy-2'-amino nucleosides can utilize N-phthaloyl protection as described by Usman *et al.*, US Patent 5,631,360, incorporated by reference
5 herein in its entirety).

During solid phase synthesis, each nucleotide is added sequentially (3'- to 5'- direction) to the solid support-bound oligonucleotide. The first nucleoside at the 3'-end of the chain is covalently attached to a solid support (e.g., controlled pore glass or polystyrene) using various linkers. The nucleotide precursor, a ribonucleoside
10 phosphoramidite, and activator are combined resulting in the coupling of the second nucleoside phosphoramidite onto the 5'-end of the first nucleoside. The support is then washed and any unreacted 5'-hydroxyl groups are capped with a capping reagent such as acetic anhydride to yield inactive 5'-acetyl moieties. The trivalent phosphorus linkage is then oxidized to a more stable phosphate linkage. At the end of the nucleotide addition
15 cycle, the 5'-O-protecting group is cleaved under suitable conditions (e.g., acidic conditions for trityl-based groups and Fluoride for silyl-based groups). The cycle is repeated for each subsequent nucleotide.

Modification of synthesis conditions can be used to optimize coupling efficiency, for example by using differing coupling times, differing reagent/phosphoramidite
20 concentrations, differing contact times, differing solid supports and solid support linker chemistries depending on the particular chemical composition of the siNA to be synthesized. Deprotection and purification of the siNA can be performed as is generally described in Deprotection and purification of the siNA can be performed as is generally
25 described in Usman *et al.*, US 5,831,071, US 6,353,098, US 6,437,117, and Bellon *et al.*, US 6,054,576, US 6,162,909, US 6,303,773, or Scaringe *supra*, incorporated by reference herein in their entireties. Additionally, deprotection conditions can be modified to provide the best possible yield and purity of siNA constructs. For example, applicant has observed that oligonucleotides comprising 2'-deoxy-2'-fluoro nucleotides
30 can degrade under inappropriate deprotection conditions. Such oligonucleotides are deprotected using aqueous methylamine at about 35°C for 30 minutes. If the 2'-deoxy-

2'-fluoro containing oligonucleotide also comprises ribonucleotides, after deprotection with aqueous methylamine at about 35°C for 30 minutes, TEA-HF is added and the reaction maintained at about 65°C for an additional 15 minutes.

Example 6: RNAi *in vitro* assay to assess siNA activity

5 An *in vitro* assay that recapitulates RNAi in a cell-free system is used to evaluate siNA constructs targeting SARS RNA targets. The assay comprises the system described by Tuschl *et al.*, 1999, *Genes and Development*, 13, 3191-3197 and Zamore *et al.*, 2000, *Cell*, 101, 25-33 adapted for use with SARS target RNA. A *Drosophila* extract derived from syncytial blastoderm is used to reconstitute RNAi activity *in vitro*. Target
10 RNA is generated via *in vitro* transcription from an appropriate SARS expressing plasmid using T7 RNA polymerase or via chemical synthesis as described herein. Sense and antisense siNA strands (for example 20 uM each) are annealed by incubation in buffer (such as 100 mM potassium acetate, 30 mM HEPES-KOH, pH 7.4, 2 mM magnesium acetate) for 1 minute at 90°C followed by 1 hour at 37°C, then diluted in
15 lysis buffer (for example 100 mM potassium acetate, 30 mM HEPES-KOH at pH 7.4, 2mM magnesium acetate). Annealing can be monitored by gel electrophoresis on an agarose gel in TBE buffer and stained with ethidium bromide. The *Drosophila* lysate is prepared using zero to two-hour-old embryos from Oregon R flies collected on yeasted molasses agar that are dechorionated and lysed. The lysate is centrifuged and the
20 supernatant isolated. The assay comprises a reaction mixture containing 50% lysate [vol/vol], RNA (10-50 pM final concentration), and 10% [vol/vol] lysis buffer containing siNA (10 nM final concentration). The reaction mixture also contains 10 mM creatine phosphate, 10 ug/ml creatine phosphokinase, 100 uM GTP, 100 uM UTP, 100 uM CTP, 500 uM ATP, 5 mM DTT, 0.1 U/uL RNasin (Promega), and 100 uM of each amino acid.
25 The final concentration of potassium acetate is adjusted to 100 mM. The reactions are pre-assembled on ice and preincubated at 25° C for 10 minutes before adding RNA, then incubated at 25° C for an additional 60 minutes. Reactions are quenched with 4 volumes of 1.25 x Passive Lysis Buffer (Promega). Target RNA cleavage is assayed by RT-PCR analysis or other methods known in the art and are compared to control reactions in
30 which siNA is omitted from the reaction.

Alternately, internally-labeled target RNA for the assay is prepared by *in vitro* transcription in the presence of [α - 32 P] CTP, passed over a G 50 Sephadex column by spin chromatography and used as target RNA without further purification. Optionally, target RNA is 5'- 32 P-end labeled using T4 polynucleotide kinase enzyme.

5 Assays are performed as described above and target RNA and the specific RNA cleavage products generated by RNAi are visualized on an autoradiograph of a gel. The percentage of cleavage is determined by PHOSPHOR IMAGER[®] (autoradiography) quantitation of bands representing intact control RNA or RNA from control reactions without siNA and the cleavage products generated by the assay.

10 In one embodiment, this assay is used to determine target sites the SARS RNA target for siNA mediated RNAi cleavage, wherein a plurality of siNA constructs are screened for RNAi mediated cleavage of the SARS RNA target, for example, by analyzing the assay reaction by electrophoresis of labeled target RNA, or by northern blotting, as well as by other methodology well known in the art.

15 Example 7: Nucleic acid inhibition of SARS target RNA *in vitro*

siNA molecules targeted to the human SARS RNA are designed and synthesized as described above. These nucleic acid molecules can be tested for cleavage activity *in vivo*, for example, using the following procedure. The target sequences and the nucleotide location within the SARS RNA are given in **Table II and III**.

20 Two formats are used to test the efficacy of siNAs targeting SARS. First, the reagents are tested in cell culture using, for example, VERO cells and/or FRhk-4 cells, to determine the extent of RNA and protein inhibition. siNA reagents (*e.g.*; see **Tables II and III**) are selected against the SARS target as described herein. RNA inhibition is measured after delivery of these reagents by a suitable transfection agent to, for example,

25 VERO cells and/or FRhk-4 cells. Relative amounts of target RNA are measured versus actin using real-time PCR monitoring of amplification (*eg.*, ABI 7700 TAQMAN[®]). A comparison is made to a mixture of oligonucleotide sequences made to unrelated targets or to a randomized siNA control with the same overall length and chemistry, but randomly substituted at each position. Primary and secondary lead reagents are chosen

30 for the target and optimization performed. After an optimal transfection agent

concentration is chosen, a RNA time-course of inhibition is performed with the lead siNA molecule. In addition, a cell-plating format can be used to determine RNA inhibition.

Delivery of siNA to Cells

5 Cells (e.g., VERO cells and/or FRhk-4 cells infected with the SARS virus) are seeded, for example, at 1×10^5 cells per well of a six-well dish in EGM-2 (BioWhittaker) the day before transfection. siNA (final concentration, for example 20nM) and cationic lipid (e.g., final concentration $2 \mu\text{g/ml}$) are complexed in EGM basal media (Bio Whittaker) at 37°C for 30 minutes in polystyrene tubes. Following vortexing, the
10 complexed siNA is added to each well and incubated for the times indicated. For initial optimization experiments, cells are seeded, for example, at 1×10^3 in 96 well plates and siNA complex added as described. Efficiency of delivery of siNA to cells is determined using a fluorescent siNA complexed with lipid. Cells in 6-well dishes are incubated with siNA for 24 hours, rinsed with PBS and fixed in 2% paraformaldehyde for 15 minutes at
15 room temperature. Uptake of siNA is visualized using a fluorescent microscope.

TAQMAN® (real-time PCR monitoring of amplification) and Lightcycler quantification of mRNA

Total RNA is prepared from cells following siNA delivery, for example, using Qiagen RNA purification kits for 6-well or Rneasy extraction kits for 96-well assays. For
20 TAQMAN® analysis (real-time PCR monitoring of amplification), dual-labeled probes are synthesized with the reporter dye, FAM or JOE, covalently linked at the 5'-end and the quencher dye TAMRA conjugated to the 3'-end. One-step RT-PCR amplifications are performed on, for example, an ABI PRISM 7700 Sequence Detector using 50 μl reactions consisting of 10 μl total RNA, 100 nM forward primer, 900 nM reverse primer,
25 100 nM probe, 1X TAQMAN® PCR reaction buffer (PE-Applied Biosystems), 5.5 mM MgCl_2 , 300 μM each dATP, dCTP, dGTP, and dTTP, 10U RNase Inhibitor (Promega), 1.25U AMPLITAQ GOLD® (DNA polymerase) (PE-Applied Biosystems) and 10U M-MLV Reverse Transcriptase (Promega). The thermal cycling conditions can consist of 30 minutes at 48°C , 10 minutes at 95°C , followed by 40 cycles of 15 seconds at 95°C
30 and 1 minute at 60°C . Quantitation of mRNA levels is determined relative to standards

generated from serially diluted total cellular RNA (300, 100, 33, 11 ng/rxn) and normalizing to β -actin or GAPDH mRNA in parallel TAQMAN® reactions (real-time PCR monitoring of amplification). For each gene of interest an upper and lower primer and a fluorescently labeled probe are designed. Real time incorporation of SYBR Green I dye into a specific PCR product can be measured in glass capillary tubes using a lightcycler. A standard curve is generated for each primer pair using control cRNA. Values are represented as relative expression to GAPDH in each sample.

Western blotting

Nuclear extracts can be prepared using a standard micro preparation technique (see for example Andrews and Faller, 1991, *Nucleic Acids Research*, 19, 2499). Protein extracts from supernatants are prepared, for example using TCA precipitation. An equal volume of 20% TCA is added to the cell supernatant, incubated on ice for 1 hour and pelleted by centrifugation for 5 minutes. Pellets are washed in acetone, dried and resuspended in water. Cellular protein extracts are run on a 10% Bis-Tris NuPage (nuclear extracts) or 4-12% Tris-Glycine (supernatant extracts) polyacrylamide gel and transferred onto nitro-cellulose membranes. Non-specific binding can be blocked by incubation, for example, with 5% non-fat milk for 1 hour followed by primary antibody for 16 hour at 4°C. Following washes, the secondary antibody is applied, for example (1:10,000 dilution) for 1 hour at room temperature and the signal detected with SuperSignal reagent (Pierce).

Example 8: RNAi mediated inhibition of SARS RNA expression

siNA constructs (e.g., siNA constructs shown in **Table III**) are tested for efficacy in reducing SARS RNA expression in, for example, VERO cells and/or FRhk-4 cells. Cells are plated approximately 24h before transfection in 96-well plates at 5,000-7,500 cells/well, 100 μ l/well, such that at the time of transfection cells are 70-90% confluent. For transfection, annealed siNAs are mixed with the transfection reagent (Lipofectamine 2000, Invitrogen) in a volume of 50 μ l/well and incubated for 20 minutes at room temperature. The siNA transfection mixtures are added to cells to give a final siNA concentration of 25 nM in a volume of 150 μ l. Each siNA transfection mixture is added to 3 wells for triplicate siNA treatments. Cells are incubated at 37° for 24h in the

continued presence of the siNA transfection mixture. At 24h, RNA is prepared from each well of treated cells. The supernatants with the transfection mixtures are first removed and discarded, then the cells are lysed and RNA prepared from each well. Target gene expression following treatment is evaluated by RT-PCR for the target gene and for a control gene (36B4, an RNA polymerase subunit) for normalization. The triplicate data is averaged and the standard deviations determined for each treatment. Normalized data are graphed and the percent reduction of target mRNA by active siNAs in comparison to their respective inverted control siNAs is determined.

In a non-limiting example, a siNA construct comprising ribonucleotides and 3'-terminal dithymidine caps is assayed along with a chemically modified siNA construct comprising 2'-deoxy-2'-fluoro pyrimidine nucleotides and purine ribonucleotides in which the sense strand of the siNA is further modified with 5' and 3'-terminal inverted deoxyabasic caps and the antisense strand comprises a 3'-terminal phosphorothioate internucleotide linkage. Additional stabilization chemistries as described in Table IV are similarly assayed for activity. These siNA constructs are compared to appropriate matched chemistry inverted controls. In addition, the siNA constructs are also compared to untreated cells, cells transfected with lipid and scrambled siNA constructs, and cells transfected with lipid alone (transfection control).

Example 9: Animal Models

Evaluating the efficacy of anti-SARS agents in animal models is an important prerequisite to human clinical trials. Byron *et al.*, 2003, *Nature*, 425, 915, describe ferret and feline animal models of SARS virus infection. Haagmans *et al.*, 2004, *Nature Medicine*, 10, 290-293, describe the use of pegylated interferon-alpha in protecting type 1 pneumocytes against SARS coronavirus infection in macaques. Gao *et al.*, 2003, *Lancet*, 362, 1895-6, describe the use of a SARS virus vaccine in monkeys. All of these models can be adapted for use for pre-clinical evaluation of the efficacy of nucleic acid compositions of the invention in modulating SARS virus gene expression toward therapeutic use.

Example 10: Indications

The present body of knowledge in SARS research indicates the need for methods to assay SARS activity and for compounds that can regulate SARS expression for research, diagnostic, and therapeutic use. As described herein, the nucleic acid molecules of the present invention can be used in assays to diagnose disease state related
5 of SARS levels. In addition, the nucleic acid molecules can be used to treat disease state related to SARS levels.

Particular degenerative and disease states that can be associated with SARS expression modulation include, but are not limited to, SARS virus infection, liver failure, hepatocellular carcinoma, cirrhosis, and/or other disease states associated with SARS
10 virus infection.

Immunomodulators, steroids, and anti-viral compounds are non-limiting examples of pharmaceutical agents that can be combined with or used in conjunction with the nucleic acid molecules (*e.g.* siNA molecules) of the instant invention. The use of ribavirin and oseltamivir are non-limiting examples of chemotherapeutic agents that can
15 be combined with or used in conjunction with the nucleic acid molecules (*e.g.* siNA molecules) of the instant invention. Those skilled in the art will recognize that other anti-cancer compounds and therapies can similarly be readily combined with the nucleic acid molecules of the instant invention (*e.g.* siNA molecules) and are hence within the scope of the instant invention.

20 Example 11: Interferons

Interferons represent a non-limiting example of a class of compounds that can be used in conjunction with the siNA molecules of the invention for treating the diseases and/or conditions described herein. Type I interferons (IFN) are a class of natural cytokines that includes a family of greater than 25 IFN- α (Pesta, 1986, *Methods*
25 *Enzymol.* 119, 3-14) as well as IFN- β , and IFN- ω . Although evolutionarily derived from the same gene (Diaz *et al.*, 1994, *Genomics* 22, 540-552), there are many differences in the primary sequence of these molecules, implying an evolutionary divergence in biologic activity. All type I IFN share a common pattern of biologic effects that begin with binding of the IFN to the cell surface receptor (Pfeffer & Strulovici, 1992,
30 Transmembrane secondary messengers for IFN- α/β . In: *Interferon. Principles and*

Medical Applications., S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.J. Stanton, and S.K. Tying, eds. 151-160). Binding is followed by activation of tyrosine kinases, including the Janus tyrosine kinases and the STAT proteins, which leads to the production of several IFN-stimulated gene products (Johnson *et al.*, 1994, *Sci. Am.* 270, 68-75). The IFN-stimulated gene products are responsible for the pleotropic biologic effects of type I IFN, including antiviral, antiproliferative, and immunomodulatory effects, cytokine induction, and HLA class I and class II regulation (Pestka *et al.*, 1987, *Annu. Rev. Biochem* 56, 727). Examples of IFN-stimulated gene products include 2-5-oligoadenylate synthetase (2-5 OAS), β_2 -microglobulin, neopterin, p68 kinases, and the Mx protein (Chebath & Revel, 1992, The 2-5 A system: 2-5 A synthetase, isospecies and functions. In: *Interferon. Principles and Medical Applications*, S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Jr. Fleischmann, T.K. Jr Hughes, G.R. Kimpel, D.W. Niesel, G.J. Stanton, and S.K. Tying, eds., pp. 225-236; Samuel, 1992, The RNA-dependent P1/eIF-2 α protein kinase. In: *Interferon. Principles and Medical Applications.* S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.H. Stanton, and S.K. Tying, eds. 237-250; Horisberger, 1992, MX protein: function and Mechanism of Action. In: *Interferon. Principles and Medical Applications.* S. Baron, D.H. Coopenhaver, F. Dianzani, W.R. Fleischmann Jr., T.K. Hughes Jr., G.R. Kimpel, D.W. Niesel, G.H. Stanton, and S.K. Tying, eds. 215-224). Although all type I IFN have similar biologic effects, not all the activities are shared by each type I IFN, and in many cases, the extent of activity varies quite substantially for each IFN subtype (Fish *et al.*, 1989, *J. Interferon Res.* 9, 97-114; Ozes *et al.*, 1992, *J. Interferon Res.* 12, 55-59). More specifically, investigations into the properties of different subtypes of IFN- α and molecular hybrids of IFN- α have shown differences in pharmacologic properties (Rubinstein, 1987, *J. Interferon Res.* 7, 545-551). These pharmacologic differences can arise from as few as three amino acid residue changes (Lee *et al.*, 1982, *Cancer Res.* 42, 1312-1316).

Eighty-five to 166 amino acids are conserved in the known IFN- α subtypes. Excluding the IFN- α pseudogenes, there are approximately 25 known distinct IFN- α subtypes. Pairwise comparisons of these nonallelic subtypes show primary sequence

differences ranging from 2% to 23%. In addition to the naturally occurring IFNs, a non-natural recombinant type I interferon known as consensus interferon (CIFN) has been synthesized as a therapeutic compound (Tong *et al.*, 1997, *Hepatology* 26, 747-754).

Interferon is currently in use for at least 12 different indications, including
5 infectious and autoimmune diseases and cancer (Borden, 1992, *N. Engl. J. Med.* 326, 1491-1492). For autoimmune diseases, IFN has been utilized for treatment of rheumatoid arthritis, multiple sclerosis, and Crohn's disease. For treatment of cancer, IFN has been used alone or in combination with a number of different compounds. Specific types of cancers for which IFN has been used include squamous cell
10 carcinomas, melanomas, hypernephromas, hemangiomas, hairy cell leukemia, and Kaposi's sarcoma. In the treatment of infectious diseases, IFNs increase the phagocytic activity of macrophages and cytotoxicity of lymphocytes and inhibits the propagation of cellular pathogens. Specific indications for which IFN has been used as treatment include hepatitis B, human papillomavirus types 6 and 11 (i.e. genital warts) (Leventhal
15 *et al.*, 1991, *N Engl J Med* 325, 613-617), chronic granulomatous disease, and SARS virus.

Pegylated interferons, i.e., interferons conjugated with polyethylene glycol (PEG), have demonstrated improved characteristics over interferon. Advantages incurred by PEG conjugation can include an improved pharmacokinetic profile compared to
20 interferons lacking PEG, thus imparting more convenient dosing regimes, improved tolerance, and improved antiviral efficacy. Such improvements have been demonstrated in clinical studies of both polyethylene glycol interferon alfa-2a (PEGASYS, Roche) and polyethylene glycol interferon alfa-2b (VIRAFERON PEG, PEG-INTRON, Enzon/Schering Plough).

25 siNA molecules in combination with interferons and polyethylene glycol interferons have the potential to improve the effectiveness of treatment of SARS or any of the other indications discussed above. siNA molecules targeting RNAs associated with SARS virus infection can be used individually or in combination with other therapies such as interferons and polyethylene glycol interferons and to achieve
30 enhanced efficacy.

Example 12: Diagnostic uses

The siNA molecules of the invention can be used in a variety of diagnostic applications, such as in the identification of molecular targets (e.g., RNA) in a variety of applications, for example, in clinical, industrial, environmental, agricultural and/or research settings. Such diagnostic use of siNA molecules involves utilizing reconstituted RNAi systems, for example, using cellular lysates or partially purified cellular lysates. siNA molecules of this invention can be used as diagnostic tools to examine genetic drift and mutations within diseased cells or to detect the presence of endogenous or exogenous, for example viral, RNA in a cell. The close relationship between siNA activity and the structure of the target RNA allows the detection of mutations in any region of the molecule, which alters the base-pairing and three-dimensional structure of the target RNA. By using multiple siNA molecules described in this invention, one can map nucleotide changes, which are important to RNA structure and function *in vitro*, as well as in cells and tissues. Cleavage of target RNAs with siNA molecules can be used to inhibit gene expression and define the role of specified gene products in the progression of disease or infection. In this manner, other genetic targets can be defined as important mediators of the disease. These experiments will lead to better treatment of the disease progression by affording the possibility of combination therapies (e.g., multiple siNA molecules targeted to different genes, siNA molecules coupled with known small molecule inhibitors, or intermittent treatment with combinations siNA molecules and/or other chemical or biological molecules). Other *in vitro* uses of siNA molecules of this invention are well known in the art, and include detection of the presence of mRNAs associated with a disease, infection, or related condition. Such RNA is detected by determining the presence of a cleavage product after treatment with a siNA using standard methodologies, for example, fluorescence resonance emission transfer (FRET).

In a specific example, siNA molecules that cleave only wild-type or mutant forms of the target RNA are used for the assay. The first siNA molecules (*i.e.*, those that cleave only wild-type forms of target RNA) are used to identify wild-type RNA present in the sample and the second siNA molecules (*i.e.*, those that cleave only mutant forms of target RNA) are used to identify mutant RNA in the sample. As reaction controls,

synthetic substrates of both wild-type and mutant RNA are cleaved by both siNA molecules to demonstrate the relative siNA efficiencies in the reactions and the absence of cleavage of the "non-targeted" RNA species. The cleavage products from the synthetic substrates also serve to generate size markers for the analysis of wild-type and mutant RNAs in the sample population. Thus, each analysis requires two siNA molecules, two substrates and one unknown sample, which is combined into six reactions. The presence of cleavage products is determined using an RNase protection assay so that full-length and cleavage fragments of each RNA can be analyzed in one lane of a polyacrylamide gel. It is not absolutely required to quantify the results to gain insight into the expression of mutant RNAs and putative risk of the desired phenotypic changes in target cells. The expression of mRNA whose protein product is implicated in the development of the phenotype (*i.e.*, disease related or infection related) is adequate to establish risk. If probes of comparable specific activity are used for both transcripts, then a qualitative comparison of RNA levels is adequate and decreases the cost of the initial diagnosis. Higher mutant form to wild-type ratios are correlated with higher risk whether RNA levels are compared qualitatively or quantitatively.

All patents and publications mentioned in the specification are indicative of the levels of skill of those skilled in the art to which the invention pertains. All references cited in this disclosure are incorporated by reference to the same extent as if each reference had been incorporated by reference in its entirety individually.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The methods and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications can be made to the invention disclosed herein without departing from the scope and spirit of the invention. Thus, such additional embodiments are within the scope of the present invention and the following claims. The present invention teaches

one skilled in the art to test various combinations and/or substitutions of chemical modifications described herein toward generating nucleic acid constructs with improved activity for mediating RNAi activity. Such improved activity can comprise improved stability, improved bioavailability, and/or improved activation of cellular responses mediating RNAi. Therefore, the specific embodiments described herein are not limiting and one skilled in the art can readily appreciate that specific combinations of the modifications described herein can be tested without undue experimentation toward identifying siNA molecules with improved RNAi activity.

The invention illustratively described herein suitably can be practiced in the absence of any element or elements, limitation or limitations that are not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments, optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the description and the appended claims.

In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

Table I: SARS virus Accession Numbers

5 LOCUS NC_004718 29736 bp ss-RNA linear VRL 15-APR-2003
DEFINITION SARS coronavirus, complete genome.
ACCESSION NC_004718

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Table II: SARS siNA and Target Sequences

SARS CoV NC_004718

Pos	Seq	Seq ID	UPos	Upper seq	Seq ID	LPos	Lower seq	Seq ID
3	ACCCAGGAAAGCCCAACCA	1	3	ACCCAGGAAAGCCCAACCA	1	21	UGGUUGGCUUUUCCUGGGU	1652
21	AACCUAGAUUUCUUGUAGA	2	21	AACCUAGAUUUCUUGUAGA	2	39	UCUACAAGAGAUUCGAGGUU	1653
39	AUCUGUUCUCUUAACGAAC	3	39	AUCUGUUCUCUUAACGAAC	3	57	GUUCGUUUAGAGAACAGAU	1654
57	CUUUAAAUCUGUGUAGCU	4	57	CUUUAAAUCUGUGUAGCU	4	75	AGCUACACAGAUUUUAAAG	1655
75	UGUCGCUCCGUGCAUGCC	5	75	UGUCGCUCCGUGCAUGCC	5	93	GGCAUGCAGCCGAGCGACA	1656
93	CUAGUGCACCUACGCAGUA	6	93	CUAGUGCACCUACGCAGUA	6	111	UACUGCGUAGGUGGACUAG	1657
111	AUAAACAUAUAAAUUUU	7	111	AUAAACAUAUAAAUUUU	7	129	AAAUUUUUUUUUUUUUU	1658
129	UACUGUGUUGACAAGAAA	8	129	UACUGUGUUGACAAGAAA	8	147	UUUCUUUGUCAACGACAGUA	1659
147	ACGAGUACUCGUCCUCU	9	147	ACGAGUACUCGUCCUCU	9	165	AGAGGACGAGUUACUCGU	1660
165	UUCUGCAGACUGCUUACGG	10	165	UUCUGCAGACUGCUUACGG	10	183	CCGUAAAGCAGUCUGCAGAA	1661
183	GUUUCGUCGUGUUGGAGU	11	183	GUUUCGUCGUGUUGGAGU	11	201	ACUGCAACACGACGAAAC	1662
201	UCGAUCAUCAGCAUACCUA	12	201	UCGAUCAUCAGCAUACCUA	12	219	UAGGUUUGCUGAUCAUGCA	1663
219	AGGUUUCGUGCGGUGUGA	13	219	AGGUUUCGUGCGGUGUGA	13	237	UCACACCGGACGAAACCU	1664
237	ACGAAAGGUAAGUAGGAG	14	237	ACGAAAGGUAAGUAGGAG	14	255	CUCCAUCUUAACCUUUCGGU	1665
255	GAGCCUUGUUCUUGGUGUC	15	255	GAGCCUUGUUCUUGGUGUC	15	273	GACACCAAGAACCAAGGCU	1666
273	CAACGAGAAACACACGUC	16	273	CAACGAGAAACACACGUC	16	291	GACGUGUUGUUCUCGUG	1667
291	CCAACUCAGUUUGCCUGUC	17	291	CCAACUCAGUUUGCCUGUC	17	309	GACAGCAAAUCUGAUUGG	1668
309	CCUUCAGGUUAGACGUG	18	309	CCUUCAGGUUAGACGUG	18	327	CACGUCUUAACCUUGAAGG	1669
327	GCUAGUGGUGGCUUGCGG	19	327	GCUAGUGGUGGCUUGCGG	19	345	CCGAAAGCCACGACUAGC	1670
345	GGACUCUGUGGAGAGGCC	20	345	GGACUCUGUGGAGAGGCC	20	363	GGCCUCUUCACAGAGUCC	1671
363	CCUACGGAGGACGUGAA	21	363	CCUACGGAGGACGUGAA	21	381	UUCACGUGCCUCCGUAUAGG	1672
381	ACACCUCAAAAUGGCACU	22	381	ACACCUCAAAAUGGCACU	22	399	AGUGCCAUUUUUGAGGUGU	1673
399	UUGUGGUCUAGUAGCGUG	23	399	UUGUGGUCUAGUAGCGUG	23	417	CAGCUCUACUAGACCACAA	1674
417	GGAAAAAGGCGUACUGCCC	24	417	GGAAAAAGGCGUACUGCCC	24	435	GGGAGUACGCCUUUUUCC	1675
435	CCAGCUUGAACAGCCCUAU	25	435	CCAGCUUGAACAGCCCUAU	25	453	AUAGGGCUGUUCAGAGCUGG	1676
453	UGUGUUCAUUAAACGUUCU	26	453	UGUGUUCAUUAAACGUUCU	26	471	AGAACGUUUAAUGAACACA	1677
471	UGAUGCCUUAAGCACCAU	27	471	UGAUGCCUUAAGCACCAU	27	489	AUUGGUGCUUAAAGGCAUCA	1678
489	UCACGGCCACAAAGGUGUU	28	489	UCACGGCCACAAAGGUGUU	28	507	AACGACCUUGUGGCGUGA	1679
507	UGAGCUGGUUGCAGAAUUG	29	507	UGAGCUGGUUGCAGAAUUG	29	525	CAUUUCUGAACCCAGCUCUA	1680
525	GGACGGCAUUCAGUACGGU	30	525	GGACGGCAUUCAGUACGGU	30	543	ACCGUACUGAAUUGCCGUCC	1681
543	UCGUAGCGGUUAACACUG	31	543	UCGUAGCGGUUAACACUG	31	561	CAGUGUUAUACCGCUACGA	1682
561	GGGAGUACUCUGGCCACAU	32	561	GGGAGUACUCUGGCCACAU	32	579	AUGUGGCACGAGUACUCCC	1683
579	UGUGGGCGAAACCCCAUU	33	579	UGUGGGCGAAACCCCAUU	33	597	AAUUGGGUUUCCGCCACA	1684
597	UGCAUACCGCAUUGUUCUU	34	597	UGCAUACCGCAUUGUUCUU	34	615	AAGAACAUUGCGGUAGUCA	1685
615	UCUUCGUAAAGACGGUAAU	35	615	UCUUCGUAAAGACGGUAAU	35	633	AUUAACGCUUACGAAGA	1686
633	UAAGGGAGCCGGUGGUCAU	36	633	UAAGGGAGCCGGUGGUCAU	36	651	AUGACCACCGGCUCCCUUA	1687

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651	UAGCUAUGGCAUCGACUA	37	651	UAGCUAUGGCAUCGACUA	37	669	UAGCUAUGGCAUCGACUA	1688
669	AAAGUCUUAUGACUUAAGGU	38	669	AAAGUCUUAUGACUUAAGGU	38	687	ACCUAAGUCUUAAGACUUA	1689
687	UGACGAGCUUGGACUAGAU	39	687	UGACGAGCUUGGACUAGAU	39	705	AUCAGUGCCAAAGCUCGUA	1690
705	UCCCAUUGAAGAUUAUGAA	40	705	UCCCAUUGAAGAUUAUGAA	40	723	UUCAUAUUAUUAUUAUGGA	1691
723	ACAAACUGGAAACACUAAG	41	723	ACAAACUGGAAACACUAAG	41	741	CUUAGUGUCCAGUUAUUGU	1692
741	GCAUGGACUGGUGGACUC	42	741	GCAUGGACUGGUGGACUC	42	759	GAGUGCACACUGCCAGUC	1693
759	CCGUGAACUCUGGUGAG	43	759	CCGUGAACUCUGGUGAG	43	777	CUCACGAGUGAGUUCACGG	1694
777	GCUCAAUGGAGGUGCAGUC	44	777	GCUCAAUGGAGGUGCAGUC	44	795	GACUGCACCUCCAUUGAGC	1695
795	CACUCGUAUGGUGGACAA	45	795	CACUCGUAUGGUGGACAA	45	813	GUUGCGCAUAGCGGAGUC	1696
813	CAUUUGUGGUGGCGCAGAU	46	813	CAUUUGUGGUGGCGCAGAU	46	831	AUCUGGGCCACAGAAUUG	1697
831	UGGGUACCCUUAUUAUGC	47	831	UGGGUACCCUUAUUAUGC	47	849	GCAUACAAGAGGGUACCCA	1698
849	CAUCAAGAUUUUCUGCA	48	849	CAUCAAGAUUUUCUGCA	48	867	UGCAGAAAUUUUUAUG	1699
867	ACGCGGGCAAGUCAAUG	49	867	ACGCGGGCAAGUCAAUG	49	885	CAUUGACUUGCCCGCGGU	1700
885	GUGCACUUAUCCGAAACAA	50	885	GUGCACUUAUCCGAAACAA	50	903	UUGUUCGGAAGAGUGCAC	1701
903	ACUUGAUUACACGAGUCG	51	903	ACUUGAUUACACGAGUCG	51	921	CGACUCGAUGAAUCAAUGU	1702
921	GAAGAGAGGUGUACUCG	52	921	GAAGAGAGGUGUACUCG	52	939	GCAGUAGACACUCUCUUC	1703
939	CUGCCGUGACCAUGAGCAU	53	939	CUGCCGUGACCAUGAGCAU	53	957	AUGCUGAGGUCACGGGAC	1704
957	UGAAUUGCCUGGUUACU	54	957	UGAAUUGCCUGGUUACU	54	975	AGUGAACCAAGCAAUUUA	1705
975	UGAGCGCUCUGUAAGAGC	55	975	UGAGCGCUCUGUAAGAGC	55	993	GCUCUUAUCAGAGCGCUCA	1706
993	CUACGAGCACACAGACCC	56	993	CUACGAGCACACAGACCC	56	1011	GGGUGUCUGGUCUCUGAG	1707
1011	CUUCGAAUUAAGAGUGCC	57	1011	CUUCGAAUUAAGAGUGCC	57	1029	GGCACUUAUUAUUAUGAAG	1708
1029	CAAGAAUUAAGACUUAAC	58	1029	CAAGAAUUAAGACUUAAC	58	1047	GAAAGUGUCAAUUAUUAUG	1709
1047	GUUUGUGUUAUUAUUAAC	59	1047	GUUUGUGUUAUUAUUAAC	59	1065	CUUUGGCAUUAUUAUUAUG	1710
1065	CUCAAAGUCUUAUUAUUA	60	1065	CUCAAAGUCUUAUUAUUA	60	1083	GUUAAAGAGAAACACAAAC	1711
1083	UCAAACACGUGUUAUUAAG	61	1083	UCAAACACGUGUUAUUAAG	61	1101	AAUGACUUAUUAUUAUUAUG	1712
1101	GAAAGACUUAUUAUUAUUA	62	1101	GAAAGACUUAUUAUUAUUA	62	1119	CUUUAACACGUGUUAUGA	1713
1119	CAUGGGGCGUUAUUAUUA	63	1119	CAUGGGGCGUUAUUAUUA	63	1137	GAAACCCUCAGUUAUUAUUA	1714
1137	UUGUACCCUGUUAUUAUUA	64	1137	UUGUACCCUGUUAUUAUUA	64	1155	AGAGCGUUAUUAUUAUUAUG	1715
1155	UCCACAGGAGUGUUAUUA	65	1155	UCCACAGGAGUGUUAUUA	65	1173	AGAUGAACAGGGUUAUUA	1716
1173	UAUGCACUUGUCUUAUUA	66	1173	UAUGCACUUGUCUUAUUA	66	1191	AUUGUUAACUUAUUAUUA	1717
1191	GAUGAAUUAUUAUUAUUA	67	1191	GAUGAAUUAUUAUUAUUA	67	1209	CAAGGUAAGACAAUGGUAU	1718
1209	CGAUGAAGUUAUUAUUA	68	1209	CGAUGAAGUUAUUAUUA	68	1227	GCAUGAAUUAUUAUUAUUA	1719
1227	GACGUGGACUUAUUAUUA	69	1227	GACGUGGACUUAUUAUUA	69	1245	UUUACAAAGUUAUUAUUA	1720
1245	AGCCACUUGUGAAUUAUUA	70	1245	AGCCACUUGUGAAUUAUUA	70	1263	UUUACAAAGUUAUUAUUA	1721
1263	UUGGACUUAUUAUUAUUA	71	1263	UUGGACUUAUUAUUAUUA	71	1281	ACAAGUUAUUAUUAUUA	1722
1281	UUGGACUUAUUAUUAUUA	72	1281	UUGGACUUAUUAUUAUUA	72	1299	AACUAAUUAUUAUUAUUA	1723
1299	UAUUAAGGACCUUAUUA	73	1299	UAUUAAGGACCUUAUUA	73	1317	UGUAGUAGGUCUUAUUA	1724
1317	AUGUGGUAUUAUUAUUA	74	1317	AUGUGGUAUUAUUAUUA	74	1335	AGUAGGUAUUAUUAUUA	1725
1335	UAUUGCUGUUAUUAUUA	75	1335	UAUUGCUGUUAUUAUUA	75	1353	CAUUAACUUAUUAUUA	1726
1353	GCAUGUCCUGGUGUUAUUA	76	1353	GCAUGUCCUGGUGUUAUUA	76	1371	UUGACAGGACGUAUUAUUA	1727
1371	AGACCCAGAUUAUUAUUA	77	1371	AGACCCAGAUUAUUAUUA	77	1389	AGGUCAAUUAUUAUUAUUA	1728
1389	UGAGCAUUAUUAUUAUUA	78	1389	UGAGCAUUAUUAUUAUUA	78	1407	AUCUGCAACACUUAUUAUUA	1729

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1407	UUUACACAAACACUCAAAC	79	1407	UUUACACAAACACUCAAAC	79	1425	GUUUGAGUGGUUGUGAUA	1730
1425	CAUUGAAACUCGACUCCGC	80	1425	CAUUGAAACUCGACUCCGC	80	1443	GCGGAGUCGAGUUUCAAUG	1731
1443	CAAGGAGGAGGACUAGA	81	1443	CAAGGAGGAGGACUAGA	81	1461	UCUAGUCUACCCUCCUUG	1732
1461	AUGUUUGGAGGUGUG	82	1461	AUGUUUGGAGGUGUG	82	1479	CACACAGCCUCCAAACAU	1733
1479	GUUUGCUAUGUUGGUGC	83	1479	GUUUGCUAUGUUGGUGC	83	1497	GCAGCCAAAGUAGGCAAC	1734
1497	CUAUAUAAGCGUGCCUAC	84	1497	CUAUAUAAGCGUGCCUAC	84	1515	GUAGGCACGCUAUUAUAG	1735
1515	CUGGCUUCUGUGCUAGU	85	1515	CUGGCUUCUGUGCUAGU	85	1533	ACUAGCAGGAGAACCCAG	1736
1533	UGCUGAUUUGGCUAGGC	86	1533	UGCUGAUUUGGCUAGGC	86	1551	GCCUGAGCCAAUAUCAGCA	1737
1551	CCAUAUGGCAUUAACUGU	87	1551	CCAUAUGGCAUUAACUGU	87	1569	ACCAGUAAUGCCAGUAUG	1738
1569	UGACAAGUGGAGACCUUG	88	1569	UGACAAGUGGAGACCUUG	88	1587	CAAGGUCUCCACAUUGCA	1739
1587	GAAUGAGGAGUCCUUGAG	89	1587	GAAUGAGGAGUCCUUGAG	89	1605	CUCAAGGAGAUCCUUAUC	1740
1605	GAUACUGAGUCGUAACGU	90	1605	GAUACUGAGUCGUAACGU	90	1623	ACGUUACGACUCAGUAUC	1741
1623	UGUUAACAUAACAUAUUGU	91	1623	UGUUAACAUAACAUAUUGU	91	1641	AACAAGUUAUAUGUUAACA	1742
1641	UGGCGAUUUUAUAUUGAAU	92	1641	UGGCGAUUUUAUAUUGAAU	92	1659	AUJCAAAUGAAAUCGCCA	1743
1659	UGAAGAGGUUGCCAUCAU	93	1659	UGAAGAGGUUGCCAUCAU	93	1677	AAUGAUGGCAACCCUUA	1744
1677	UUUGGCAUCUUCUCUGCU	94	1677	UUUGGCAUCUUCUCUGCU	94	1695	AGCAGAGAAAAGUAGCCAAA	1745
1695	UUCUACAAGUGCCUUAU	95	1695	UUCUACAAGUGCCUUAU	95	1713	AAUAAAGGCACUUGUAGAA	1746
1713	UGACACUAUAAAGAGUCU	96	1713	UGACACUAUAAAGAGUCU	96	1731	AAGACUUAUAUAGUGUCA	1747
1731	UGAUUAACAGUCUUUCAA	97	1731	UGAUUAACAGUCUUUCAA	97	1749	UUUGAAAGACUUGUAUCA	1748
1749	AACCAUUGUUGGUCUCC	98	1749	AACCAUUGUUGGUCUCC	98	1767	GCAGGACACUACAAGUGGU	1749
1767	CGGUAAUAUAAAGUUAAC	99	1767	CGGUAAUAUAAAGUUAAC	99	1785	GGUAAUUAUAUAGUUAACCG	1750
1785	CAAGGAAAGCCCGUAA	100	1785	CAAGGAAAGCCCGUAA	100	1803	UUUUAAGGCGUUAUCCUUG	1751
1803	AGGUGCUUGGAACAUUGGA	101	1803	AGGUGCUUGGAACAUUGGA	101	1821	UCCAAUUGUCCAAAGCACCU	1752
1821	ACAACAGAGAUCAUUAUA	102	1821	ACAACAGAGAUCAUUAUA	102	1839	UAAACUGAUCUCUGUUGU	1753
1839	AACACCACUGUGGUAU	103	1839	AACACCACUGUGGUAU	103	1857	AAACCCACACAGUGGUGUU	1754
1857	UCCUCACAGGUCUGUGU	104	1857	UCCUCACAGGUCUGUGU	104	1875	ACCAGCAGCCUGUGAGGGA	1755
1875	UGUUAUCAGAUCAUUAU	105	1875	UGUUAUCAGAUCAUUAU	105	1893	AAAAUUGAUCUGUAUAACA	1756
1893	UGCGCGCACACUUGAUGCA	106	1893	UGCGCGCACACUUGAUGCA	106	1911	UGCAUCAAGUGUGCGCGCA	1757
1911	AGCAAACCAUUAUUAUCCU	107	1911	AGCAAACCAUUAUUAUCCU	107	1929	AGGAAUUGAGUGGUUUUGCU	1758
1929	UGAUUUGCAAAGAGCAGCU	108	1929	UGAUUUGCAAAGAGCAGCU	108	1947	AGCUGCUCUUUGCAAUAUCA	1759
1947	UGUCACCAUAUUAUGUGU	109	1947	UGUCACCAUAUUAUGUGU	109	1965	ACCAUCAAGUAUGGUGACA	1760
1965	UAUUUCUGAACAGUUAUA	110	1965	UAUUUCUGAACAGUUAUA	110	1983	UAUAGACUGUUCAGAAUA	1761
1983	ACGUCUUGUCGACGCGCAUG	111	1983	ACGUCUUGUCGACGCGCAUG	111	2001	CAUGGCGUCGACAAGACGU	1762
2001	GGUUUAUUAUUAUUAUUAU	112	2001	GGUUUAUUAUUAUUAUUAU	112	2019	CAGGUCUGAAGUAUAAACC	1763
2019	GCUCACCAACAGUGUUAU	113	2019	GCUCACCAACAGUGUUAU	113	2037	AUGACACUGUUGGUGAGC	1764
2037	UAUUUGGCAUAUUAUUAU	114	2037	UAUUUGGCAUAUUAUUAU	114	2055	AGUUAUAUUGCCAUUAUA	1765
2055	UGGUGGUCUUAUUAUUAU	115	2055	UGGUGGUCUUAUUAUUAU	115	2073	CUGUUGUAACAAGACCACA	1766
2073	GACUUCUUAUUAUUAUUAU	116	2073	GACUUCUUAUUAUUAUUAU	116	2091	AGAACCCACUCAGAGAUUC	1767
2091	UAUUCUUUUGGCGACUUAU	117	2091	UAUUCUUUUGGCGACUUAU	117	2109	AGUAGUCCCAAAAGAUUA	1768
2109	UGUUGAAACACUAGGCGCU	118	2109	UGUUGAAACACUAGGCGCU	118	2127	AGGCCUGAGUUUUUAACA	1769
2127	UAUCUUUGAAUGGAUUGAG	119	2127	UAUCUUUGAAUGGAUUGAG	119	2145	CUCAAUCCAUUCAAAGUA	1770
2145	GGCGAAACUUAUGGACGGA	120	2145	GGCGAAACUUAUGGACGGA	120	2163	UCCUGCACUAAGUUUCCGCC	1771

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2163	AGUUGAAUUCUCAAGGAU	121	2163	AGUUGAAUUCUCAAGGAU	121	2181	AUCCUUGAGAAAUUCAACU	1772
2181	UGCUUGGGAGAUUCUCAA	122	2181	UGCUUGGGAGAUUCUCAA	122	2199	UUUGAGAUCCUCCAGCA	1773
2199	AUUUCUUAUACUAGGUU	123	2199	AUUUCUUAUACUAGGUU	123	2217	AACACCUUGAUAGAGAAU	1774
2217	UUUUGACAUUCUCAAGGU	124	2217	UUUUGACAUUCUCAAGGU	124	2235	ACCCUUGACGAUGUCAA	1775
2235	UCAAUACAGGUUGCUUA	125	2235	UCAAUACAGGUUGCUUA	125	2253	UGAAGCAACCGUAAUUGA	1776
2253	AGAAUACUACAGGAUUG	126	2253	AGAAUACUACAGGAUUG	126	2271	ACAACCUUGAUUGUUAUCU	1777
2271	UGUAAAUGCUUAUUGAU	127	2271	UGUAAAUGCUUAUUGAU	127	2289	AUCAUAGAGCAUUAUACA	1778
2289	UGUUGUUAACAAGGCACUC	128	2289	UGUUGUUAACAAGGCACUC	128	2307	GAGUGCCUUGUUAACAACA	1779
2307	CGAAUUGUCAUUGAUCAA	129	2307	CGAAUUGUCAUUGAUCAA	129	2325	UUGAUCAUUGCACAUAUUG	1780
2325	AGUCACUACGUGGCGCA	130	2325	AGUCACUACGUGGCGCA	130	2343	UGCAGCAAGCAUAGUAGCU	1781
2343	AAAGUUGGCAUACUACAAC	131	2343	AAAGUUGGCAUACUACAAC	131	2361	GUUGAGUAGCGCAACUUAU	1782
2361	CUUAGGUGAAGUCUUAUC	132	2361	CUUAGGUGAAGUCUUAUC	132	2379	GAUGAAGACUUCACCUAAG	1783
2379	CGCUCAAAGCAAGGGACUU	133	2379	CGCUCAAAGCAAGGGACUU	133	2397	AAGUCCCUUGCUUUGAGCG	1784
2397	UUACCGUCAGUGUAUACGU	134	2397	UUACCGUCAGUGUAUACGU	134	2415	ACGUUAACACUGACGGUAA	1785
2415	UGGCAAGGAGCGUGCAA	135	2415	UGGCAAGGAGCGUGCAA	135	2433	UUGCAGCUGCCUUGCCCA	1786
2433	ACUACUACUCCUUAUAG	136	2433	ACUACUACUCCUUAUAG	136	2451	CUUAGAGGCAUGAGUAGU	1787
2451	GGCACCACAAAGAAUAACC	137	2451	GGCACCACAAAGAAUAACC	137	2469	GGUUAUUCUUAUUGGUGCC	1788
2469	CUUUCUUGAAGGUGAUUA	138	2469	CUUUCUUGAAGGUGAUUA	138	2487	UGAAUACCCUUCACAGAAAG	1789
2487	ACAAGACACAGUACUUAAC	139	2487	ACAAGACACAGUACUUAAC	139	2505	GGUAAUACUUGUGUCAUGU	1790
2505	CUCUGAGGAGGUUUCUC	140	2505	CUCUGAGGAGGUUUCUC	140	2523	GAGAACAACCCUCCACAG	1791
2523	CAAGAACGGUGAACUCGAA	141	2523	CAAGAACGGUGAACUCGAA	141	2541	UUCGAGUUCACCGUUCUUG	1792
2541	AGCACUGGAGACGCCGUU	142	2541	AGCACUGGAGACGCCGUU	142	2559	AACGGCGUCUCGAGUGCU	1793
2559	UGAUAGCUUACACAAUUGGA	143	2559	UGAUAGCUUACACAAUUGGA	143	2577	UCCAUUUGUGAAGCUUAUA	1794
2577	AGCUAUCGUCGGCACACCA	144	2577	AGCUAUCGUCGGCACACCA	144	2595	UGGUGUGCCGACGAUAGCU	1795
2595	AGUCUGUGUAAUUGGCCUC	145	2595	AGUCUGUGUAAUUGGCCUC	145	2613	GAGGCCAUUUAACACAGACU	1796
2613	CAUGCUCUUAAGAGAUUAAG	146	2613	CAUGCUCUUAAGAGAUUAAG	146	2631	CUUAAUCUCUUAAGAGAUAG	1797
2631	GGACAAAGAAACAAUACUGC	147	2631	GGACAAAGAAACAAUACUGC	147	2649	GCAGUUAUUGUUCUUGUCC	1798
2649	CGCAUUGUCUCCUGGUUUA	148	2649	CGCAUUGUCUCCUGGUUUA	148	2667	UAAACCCAGGAGACAAUUGCG	1799
2667	ACUGGCUACAAACAAUUGUC	149	2667	ACUGGCUACAAACAAUUGUC	149	2685	GACAUUGUUAUUGAGCCAGU	1800
2685	CUUUCGCUUAAAGGGGGU	150	2685	CUUUCGCUUAAAGGGGGU	150	2703	ACCCCUUUAAGCGGAAAG	1801
2703	UGCACCAUUAAGGGUGUA	151	2703	UGCACCAUUAAGGGUGUA	151	2721	UACACCUUUAUUGGUGCA	1802
2721	AACCUUUGGAGAGAUACU	152	2721	AACCUUUGGAGAGAUACU	152	2739	AGUAUCUUCUCCAAAGGUU	1803
2739	UGUUGGGAGUUAUUAAGGU	153	2739	UGUUGGGAGUUAUUAAGGU	153	2757	ACCUUGAACUUCGCCAAACA	1804
2757	UUACAAGAAUGUGAGAAUC	154	2757	UUACAAGAAUGUGAGAAUC	154	2775	GAUUCUCACAUUCUUGUAA	1805
2775	CACAUUUGAGCUUUAUGAA	155	2775	CACAUUUGAGCUUUAUGAA	155	2793	UUCAUCUACUUAUUGGUG	1806
2793	ACGUUGUAGACAAAGUGCUU	156	2793	ACGUUGUAGACAAAGUGCUU	156	2811	AAGCACUUAUUGCAACACGU	1807
2811	UAUUGAAAGUGCUCUGUC	157	2811	UAUUGAAAGUGCUCUGUC	157	2829	GACGAGCAGUUAUUAUA	1808
2829	CUACACUGUUAUUAUCCGU	158	2829	CUACACUGUUAUUAUCCGU	158	2847	ACCGAUUAACACAGUAG	1809
2847	UACCGAAGUUAUUAUUAU	159	2847	UACCGAAGUUAUUAUUAU	159	2865	AAACUCAGUUAUUAUUAU	1810
2865	UGCAUGUGUUAUUAUUAU	160	2865	UGCAUGUGUUAUUAUUAU	160	2883	CUCUGUUAACACACAGCA	1811
2883	GGCUGUUGUUAUUAUUAU	161	2883	GGCUGUUGUUAUUAUUAU	161	2901	UAAAGUCUUAACACAGCC	1812
2901	ACAACCAAGUUAUUAUUAU	162	2901	ACAACCAAGUUAUUAUUAU	162	2919	GAGAUACAGAAACUUGUUG	1813

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2919	CCUACCAACAUGGGUAAU	163	2919	CCUACCAACAUGGGUAAU	163	2937	AAUACCCAUUGUUGAAAG	1814
2937	UGAUCUUGAGAGUGGAGU	164	2937	UGAUCUUGAGAGUGGAGU	164	2955	ACUCCACUCAAGCAUCA	1815
2955	UGUAGCUACAUUCUACUUA	165	2955	UGUAGCUACAUUCUACUUA	165	2973	UUAAGUAGUAGUAGCAUCA	1816
2973	AUUUGAUGAGCUGGUGAA	166	2973	AUUUGAUGAGCUGGUGAA	166	2991	UUCACAGCAUCAUCAAU	1817
2991	AGAAAACUUAUACACGU	167	2991	AGAAAACUUAUACACGU	167	3009	ACGUGAUGAAAAGUUUCU	1818
3009	UAUGUAUUGUUCUUUAC	168	3009	UAUGUAUUGUUCUUUAC	168	3027	GUAAAAGGAACAAUACAUA	1819
3027	CCUCCAGAUAGGAGAA	169	3027	CCUCCAGAUAGGAGAA	169	3045	UUCUCCUCAUCUGGAGG	1820
3045	AGAGGAGAGGAGAGUGU	170	3045	AGAGGAGAGGAGAGUGU	170	3063	ACACUCUGCAUCGUCUUCU	1821
3063	UGAGGAGAGGAGAGAGUGU	171	3063	UGAGGAGAGGAGAGAGUGU	171	3081	AUCAUUCUUCUUCUCA	1822
3081	UGAAACCUUGAGAACAGAG	172	3081	UGAAACCUUGAGAACAGAG	172	3099	CUCAUGUUCACAGGUUUA	1823
3099	GUACGGUACAGAGGAGAU	173	3099	GUACGGUACAGAGGAGAU	173	3117	AUCAUCCUCUGUACCGUAC	1824
3117	UUAUCAAGGUCUCCUCUG	174	3117	UUAUCAAGGUCUCCUCUG	174	3135	CAGAGGAGACCUUGAUAA	1825
3135	GGAAUUGGUGCCUCAGCU	175	3135	GGAAUUGGUGCCUCAGCU	175	3153	AGCUGAGGCACCAAUUCC	1826
3153	UGAAACAGUUCGAGUUGAG	176	3153	UGAAACAGUUCGAGUUGAG	176	3171	CUCAUCUGAACUGUUUA	1827
3171	GGAAAGAGAGAGGAGAC	177	3171	GGAAAGAGAGAGGAGAC	177	3189	GUCUCCUCUUCUUCUCC	1828
3189	CUGGCUUGAGUAUACUACU	178	3189	CUGGCUUGAGUAUACUACU	178	3207	AGUAGUAUCAUCCAGCCAG	1829
3207	UGAGCAUUCAGAGUUGAG	179	3207	UGAGCAUUCAGAGUUGAG	179	3225	CUCAUCUCUGAUUGUCA	1830
3225	GCCAGAACAGAACCUACA	180	3225	GCCAGAACAGAACCUACA	180	3243	UGAGGUUCUGGUUCUGGC	1831
3243	ACCUGAAGAACAGUUAU	181	3243	ACCUGAAGAACAGUUAU	181	3261	AUAAACAGGUAUAAUGGA	1832
3261	UCAGUUUACUGGUUAUUA	182	3261	UCAGUUUACUGGUUAUUA	182	3279	UAAUAAACAGGUAUAAUGGA	1833
3279	AAAACUACUGACAAUGUU	183	3279	AAAACUACUGACAAUGUU	183	3297	AACAUUGUCAGUAAUGUUU	1834
3297	UGCCAUUAAUGUUGUAC	184	3297	UGCCAUUAAUGUUGUAC	184	3315	GUCAACACAUUAAUGGCA	1835
3315	CAUCGUUAAAGAGGACAA	185	3315	CAUCGUUAAAGAGGACAA	185	3333	UUGUCCUCCUUAAGCAUG	1836
3333	AAGUGCUAAUCCUAGGUG	186	3333	AAGUGCUAAUCCUAGGUG	186	3351	CACCAUAGGUAUAGCACUU	1837
3351	GAUUGUAAUUGCUGUAAC	187	3351	GAUUGUAAUUGCUGUAAC	187	3369	GUUAGCAGCAUUAUACAUC	1838
3369	CAUACACCUUGAAGGUGCA	188	3369	CAUACACCUUGAAGGUGCA	188	3387	ACCAUGUUCAGGUGUAUG	1839
3387	UGGUGGUGUAGCAGGUGCA	189	3387	UGGUGGUGUAGCAGGUGCA	189	3405	UGCACCUUGCUACACCA	1840
3405	ACUCAACAAGGCAACCAU	190	3405	ACUCAACAAGGCAACCAU	190	3423	AUUGGUUCCUUGUUGAGU	1841
3423	UGGUGCCAUGCAAAAGGAG	191	3423	UGGUGCCAUGCAAAAGGAG	191	3441	CUCUUIUUGCAUGGACCA	1842
3441	GAGUGAUGAUUAUUAAG	192	3441	GAGUGAUGAUUAUUAAG	192	3459	CUUAAUGUAUUAUUAUUA	1843
3459	GCUAAUUGGCCUUAUUA	193	3459	GCUAAUUGGCCUUAUUA	193	3477	UGUAAAGGAGGCAUUAAGC	1844
3477	AGUAGGAGGUGUUGUUG	194	3477	AGUAGGAGGUGUUGUUG	194	3495	CAACAAGACCCUCCUUAU	1845
3495	GCUUUCUGGAGCAUUAUCU	195	3495	GCUUUCUGGAGCAUUAUCU	195	3513	AAGAUUAUGUCCAGAAAGC	1846
3513	UGCUAAGAAGUGUCUGCAU	196	3513	UGCUAAGAAGUGUCUGCAU	196	3531	AUGCAGACACUUCUUAAGCA	1847
3531	UGUUGUUGGAGGUUAACCUA	197	3531	UGUUGUUGGAGGUUAACCUA	197	3549	JAGGUUAGGUCCAAACA	1848
3549	AAUUGCAGGUGAGGACAU	198	3549	AAUUGCAGGUGAGGACAU	198	3567	GAUGUCCUACCCUUGCAU	1849
3567	CCAGCUUCUUAAGGCAGCA	199	3567	CCAGCUUCUUAAGGCAGCA	199	3585	UGCUGCCUUAAGAAAGCUGG	1850
3585	AUAUGAAAUAUUAUUA	200	3585	AUAUGAAAUAUUAUUA	200	3603	UGAAUUGAAAUAUUAUUA	1851
3603	ACAGGACAUUAUUAUUA	201	3603	ACAGGACAUUAUUAUUA	201	3621	UGCAAAGUAAGUAGUCCUGU	1852
3621	ACCAUUGUUGCAGCAGGC	202	3621	ACCAUUGUUGCAGCAGGC	202	3639	GCCUGCUGACAAUUAUGG	1853
3639	CAUUAUUGGUGCUAAACCA	203	3639	CAUUAUUGGUGCUAAACCA	203	3657	UGGUUAGCACCACAAUUAUG	1854
3657	ACUUCAGUCUUUAACAAGU	204	3657	ACUUCAGUCUUUAACAAGU	204	3675	CACUUGUAAAGACUGAAGU	1855

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3675	GUGCGUGCAGACGGUUCGU	205	3675	GUGCGUGCAGACGGUUCGU	205	3693	ACGAACCGUCUGCAGGCAC	1856
3693	UACACAGGUUUUAUUGCA	206	3693	UACACAGGUUUUAUUGCA	206	3711	UGCAAUUAUAAACCCUGUA	1857
3711	AGUAAUGACAAAGUCUUCU	207	3711	AGUAAUGACAAAGUCUUCU	207	3729	AAGAGCUUUUGUCAUAGCU	1858
3729	UUAUGAGCAGUUGUCUAG	208	3729	UUAUGAGCAGUUGUCUAG	208	3747	CAGACAAACCCUGCUCAUA	1859
3747	GGAUUAUCUUUAUAAACUG	209	3747	GGAUUAUCUUUAUAAACUG	209	3765	CAGGUUAUCAAAGUAUCC	1860
3765	GAAAGCCUAGAGUGGAAGCA	210	3765	GAAAGCCUAGAGUGGAAGCA	210	3783	UGCUUCCACUCUAGGCUUC	1861
3783	ACCUAAACAAGAGGAGCCA	211	3783	ACCUAAACAAGAGGAGCCA	211	3801	UGGUCUCUCUUGUUUAGGU	1862
3801	ACCAACACACAGAAUUC	212	3801	ACCAACACACAGAAUUC	212	3819	GGAAUCUUCUGUUUUGGU	1863
3819	CAAAACUGAGGAGAAUCU	213	3819	CAAAACUGAGGAGAAUCU	213	3837	AGAUUUCUCCUCAGUUUUG	1864
3837	UGUCGUACAGAGCCUGUC	214	3837	UGUCGUACAGAGCCUGUC	214	3855	GACAGGCUUCUGUACGACA	1865
3855	CGAUGUGAAGCCAAAUUU	215	3855	CGAUGUGAAGCCAAAUUU	215	3873	AAUUUUUGGCUUCACAUCC	1866
3873	UAAAGCCUGCAUUGAUGAG	216	3873	UAAAGCCUGCAUUGAUGAG	216	3891	CUCAUCAUUGCAGGCCUUA	1867
3891	GGUUAACCAACACUGGAA	217	3891	GGUUAACCAACACUGGAA	217	3909	UUCAGAGUUGUUGGUAACC	1868
3909	AGAAACUAGUUCUUAAC	218	3909	AGAAACUAGUUCUUAAC	218	3927	GGUAAAGAAACUUAUUAUCU	1869
3927	CAUAAGUUAUCUUGUUU	219	3927	CAUAAGUUAUCUUGUUU	219	3945	AAACAAGAGUAACUUAUUG	1870
3945	UGCUGAUUAUAAUGGUAAG	220	3945	UGCUGAUUAUAAUGGUAAG	220	3963	CUUACCAUUGAUUAUCAGCA	1871
3963	GCUUUACCAUGAUUCUCAG	221	3963	GCUUUACCAUGAUUCUCAG	221	3981	CUGAGAAUCAUGGUAAGC	1872
3981	GAACAUGCUUAGAGGUGAA	222	3981	GAACAUGCUUAGAGGUGAA	222	3999	UUCACCUCUUAAGCAUUGC	1873
3999	AGAUAGUCUUUCCUUGAG	223	3999	AGAUAGUCUUUCCUUGAG	223	4017	CUCAAGGAAAGACAUUUCU	1874
4017	GAAAGGACCCUUAUACUG	224	4017	GAAAGGACCCUUAUACUG	224	4035	CAUGUAGGUGACUCCUUC	1875
4035	GGUAGGUGCAUUAUCACU	225	4035	GGUAGGUGCAUUAUCACU	225	4053	AGUGAUUAUACUCCUACC	1876
4053	UAGUGGUGAUUAUCUUGU	226	4053	UAGUGGUGAUUAUCUUGU	226	4071	ACAAUGUAUUAUACCCACUA	1877
4071	UGUUGUAUUAUACCCUAAA	227	4071	UGUUGUAUUAUACCCUAAA	227	4089	UUUGAGGGUUAUUAACAACA	1878
4089	AAAGGCUGGUGGCACUACU	228	4089	AAAGGCUGGUGGCACUACU	228	4107	AGUAGUGCCACCCAGCCUUC	1879
4107	UGAGUAGCUCUACAGAGCU	229	4107	UGAGUAGCUCUACAGAGCU	229	4125	AGUCUUUGAGAGCAUCUCA	1880
4125	UUUGAAGAAAGUGCCAGUU	230	4125	UUUGAAGAAAGUGCCAGUU	230	4143	AACUGGCACUUUCUUCUAAA	1881
4143	UGAUGAGUAUAUAAACACG	231	4143	UGAUGAGUAUAUAAACACG	231	4161	CGUGGUUAUAUACUACA	1882
4161	GUACCCUGGACAAAGGAUGU	232	4161	GUACCCUGGACAAAGGAUGU	232	4179	ACAUCCUUGUCCAGGGUAC	1883
4179	UGCUGGUUAUACACUUGAG	233	4179	UGCUGGUUAUACACUUGAG	233	4197	CUCAAGUGUAUAACCCAGCA	1884
4197	GGAAGCUAAGACUGCUCUU	234	4197	GGAAGCUAAGACUGCUCUU	234	4215	AAGAGCAGUCUUAGCUUCC	1885
4215	UAAGAAUUGCAAAUUCUGCA	235	4215	UAAGAAUUGCAAAUUCUGCA	235	4233	UGCAGAUUUUGCAUUUCUUA	1886
4233	AUUUAUGUACUACCUUUA	236	4233	AUUUAUGUACUACCUUUA	236	4251	UGAAGGUAGUACAUAAAAU	1887
4251	AGAAGCACCUAUUGCUAAG	237	4251	AGAAGCACCUAUUGCUAAG	237	4269	CUUAGCAUUAAGGUCUUCU	1888
4269	GGAAGAGAUUCUAGGAACU	238	4269	GGAAGAGAUUCUAGGAACU	238	4287	AGUCCUAGAAUGUCUUCUCC	1889
4287	UGUAUCCUGGAAUUAUGAGA	239	4287	UGUAUCCUGGAAUUAUGAGA	239	4305	UCUCAAAUCCAGGAUACA	1890
4305	AGAAUAGCUUGCUCUAGCU	240	4305	AGAAUAGCUUGCUCUAGCU	240	4323	AGCAUGAGCAAGCAUUUCU	1891
4323	UAGAAGACAAAGAAAUUA	241	4323	UAGAAGACAAAGAAAUUA	241	4341	UAUUUUUCUUGUCUCUUA	1892
4341	AAUGCCUAUAUAGCAUGGAU	242	4341	AAUGCCUAUAUAGCAUGGAU	242	4359	AUCCAUGCAUAUAGGCAU	1893
4359	UGUAGAGCCAAUAAUGGCA	243	4359	UGUAGAGCCAAUAAUGGCA	243	4377	UGCAUUUAUGGCUCAACA	1894
4377	AACCAUCCAAACGUAAGUAU	244	4377	AACCAUCCAAACGUAAGUAU	244	4395	AUACUUAACGUUGGUAU	1895
4395	UAAAGGAUUUAAAAUCAA	245	4395	UAAAGGAUUUAAAAUCAA	245	4413	UUGAAUUUUUAUUCUUA	1896
4413	AGAGGGCAUCGUUGACUAU	246	4413	AGAGGGCAUCGUUGACUAU	246	4431	AUAGUCAACGAUGGCCUUCU	1897

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4431	UGGUGUCCGAUUCUUCUUU	247	4431	UGGUGUCCGAUUCUUCUUU	247	4449	AAAGAAGAAUCGGACACCA	1898
4449	UUUAUACUAGUAAAGAGCCU	248	4449	UUUAUACUAGUAAAGAGCCU	248	4467	AGGCUCUUUACUAGUAUA	1899
4467	UGUAGCUUCUUAUUAUACG	249	4467	UGUAGCUUCUUAUUAUACG	249	4485	CGUAUAUUAAGAAAGCUACA	1900
4485	GAAGCUCUACUUCUUAUUA	250	4485	GAAGCUCUACUUCUUAUUA	250	4503	AUUUAGAGAGUUCAGCUUC	1901
4503	UGAGCCGCUUGUCACAAUG	251	4503	UGAGCCGCUUGUCACAAUG	251	4521	CAUUGAGACAAGCGGCUCA	1902
4521	GCCAAUUGGUUAUGUGACA	252	4521	GCCAAUUGGUUAUGUGACA	252	4539	UGUCACAUAAACCAUUGGC	1903
4539	ACAUGGUUUUAUUAUUAUUA	253	4539	ACAUGGUUUUAUUAUUAUUA	253	4557	UUCAAGAUUAAACCAUGU	1904
4557	AGAGGUGCGCGCUGUAUG	254	4557	AGAGGUGCGCGCUGUAUG	254	4575	CAUACAGCGCGCAGCCUCU	1905
4575	GCGUUCUCUUAAGCUCUCU	255	4575	GCGUUCUCUUAAGCUCUCU	255	4593	AGGAGCUUUAAGAGAACGC	1906
4593	UGCCGUAUGUCAGUAUCA	256	4593	UGCCGUAUGUCAGUAUCA	256	4611	UGAUACUGACACUACGGCA	1907
4611	AUCACCAGAUGCUGUUAUCU	257	4611	AUCACCAGAUGCUGUUAUCU	257	4629	AGUAACAGCAUCUGGUGAU	1908
4629	UACAUUAUUAUGGAUACCU	258	4629	UACAUUAUUAUGGAUACCU	258	4647	GAGUAUCCAUUAUUAUGUA	1909
4647	CACUUCGUAUCAAAAGACA	259	4647	CACUUCGUAUCAAAAGACA	259	4665	UGUCUUAUGAGCAGGAUG	1910
4665	AUCUGAGGAGCACUUAUGUA	260	4665	AUCUGAGGAGCACUUAUGUA	260	4683	UACAAAGUGCUCCUCAGAU	1911
4683	AGAAACAGUUUCUUAUGGCU	261	4683	AGAAACAGUUUCUUAUGGCU	261	4701	AGCCAAAGAAACUGUUUCU	1912
4701	UGGCUCUUAACAGAUUUGG	262	4701	UGGCUCUUAACAGAUUUGG	262	4719	CCAUCUCUGUAAGAGGCCA	1913
4719	GUCCUUAUCAGGACAGCGU	263	4719	GUCCUUAUCAGGACAGCGU	263	4737	ACGCUGUCCUGAAUAGGAC	1914
4737	UACAGAGUUAAGUGUUAUA	264	4737	UACAGAGUUAAGUGUUAUA	264	4755	UUCAACACCUAAACUCUGUA	1915
4755	AUUUCUUAAGCGUGGUGAC	265	4755	AUUUCUUAAGCGUGGUGAC	265	4773	GUCACCACGCUUAAGAAAU	1916
4773	CAAAUUGUGUACCCACACU	266	4773	CAAAUUGUGUACCCACACU	266	4791	AGUGUGUAACAAUUAUUG	1917
4791	UCUGGAGGCCCCGUCGAG	267	4791	UCUGGAGGCCCCGUCGAG	267	4809	CUCGACGGGCUCCUCCAGA	1918
4809	GUUUAUUCUAGCGGUGAG	268	4809	GUUUAUUCUAGCGGUGAG	268	4827	CUCACCGUACAGUAAGAAC	1919
4827	GGUUCUUAACUUAAGACAAA	269	4827	GGUUCUUAACUUAAGACAAA	269	4845	UUUGUCAAGUGAAAGAAC	1920
4845	ACUAAAGAGUCUCUUAUCC	270	4845	ACUAAAGAGUCUCUUAUCC	270	4863	GGAUAGAGACUCUUAUAGU	1921
4863	CCUGCGGAGGUUAAGACU	271	4863	CCUGCGGAGGUUAAGACU	271	4881	AGUCUUAACUCCCGCAGG	1922
4881	UAUAAAAGUGUACACACU	272	4881	UAUAAAAGUGUACACACU	272	4899	AGUUGAGAACACUUAUUA	1923
4899	UGUGGACAAACACUUAUCUC	273	4899	UGUGGACAAACACUUAUCUC	273	4917	GAGUUAUGUUGUCCACA	1924
4917	CCACACACAGCUUUGGUAU	274	4917	CCACACACAGCUUUGGUAU	274	4935	AUCCACAAGCUGUGUGG	1925
4935	UAUGUCUAUGACAUUAUGGA	275	4935	UAUGUCUAUGACAUUAUGGA	275	4953	UCCAUAUGUACUAAGACUA	1926
4953	ACAGCAGUUAUGUCCAAACA	276	4953	ACAGCAGUUAUGUCCAAACA	276	4971	UGUUGGACCAACUCCUGU	1927
4971	AUACUUGGAUGGUGCUGAU	277	4971	AUACUUGGAUGGUGCUGAU	277	4989	AUCAGCACCACUCCAAAGUAU	1928
4989	UGUUAACAAAUAUUAUUAUUA	278	4989	UGUUAACAAAUAUUAUUAUUA	278	5007	AGGUUUAUUUUUUGUAACA	1929
5007	UCAUGUAAAUAUGAGGGU	279	5007	UCAUGUAAAUAUGAGGGU	279	5025	ACCCUACUUAUUUUAUUAUGA	1930
5025	UAAGACUUAUUUUAUUAUUA	280	5025	UAAGACUUAUUUUAUUAUUA	280	5043	UAGUACAAAGAAAGUCUUA	1931
5043	ACCUAGUGAUGACACACUA	281	5043	ACCUAGUGAUGACACACUA	281	5061	UAGUGUGUACUACUAGGU	1932
5061	ACGUAGUGAAGCUUUCGAG	282	5061	ACGUAGUGAAGCUUUCGAG	282	5079	CUCGAAAGCUUACUACGU	1933
5079	GUACUACCAUACUUCUUAUGAU	283	5079	GUACUACCAUACUUCUUAUGAU	283	5097	AUCAAGGUUAUGGUUAC	1934
5097	UGAGAGUUUUCUUGUAGG	284	5097	UGAGAGUUUUCUUGUAGG	284	5115	CCUACCAAGAAACUCUCA	1935
5115	GUACAGUUCUGCUUUAUAAAC	285	5115	GUACAGUUCUGCUUUAUAAAC	285	5133	GUUUAAGCAGACUAGUAC	1936
5133	CCACACAAAGAAUUGGAAA	286	5133	CCACACAAAGAAUUGGAAA	286	5151	UUUCCAUUUUUUUGUGG	1937
5151	AUUUCCUCAAAGUUGGUGU	287	5151	AUUUCCUCAAAGUUGGUGU	287	5169	ACCACCAACUUGAGGAAU	1938
5169	UUUAAACUUAUUUAUUAUGG	288	5169	UUUAAACUUAUUUAUUAUGG	288	5187	CCAUIUUAUUGAAUUAUUA	1939

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5187	GGCUGAAUACAAUUGUUAU	289	5187	GGCUGAAUACAAUUGUUAU	289	5205	AUAACAAUUGUUAUACAGCC	1940
5205	UUUGUCUAGUGUUUUUAUA	290	5205	UUUGUCUAGUGUUUUUAUA	290	5223	UAAUAAAACACUAGACAAA	1941
5223	AGCACUUAACAGCUUGAA	291	5223	AGCACUUAACAGCUUGAA	291	5241	UUCAGCUGUUUGAAGUCU	1942
5241	AGUCAAUUAUUGACCA	292	5241	AGUCAAUUAUUGACCA	292	5259	UGGUGCAUUGAAUUGACU	1943
5259	AGCACUUAACAGGCUUAU	293	5259	AGCACUUAACAGGCUUAU	293	5277	AUAAGCCUUAUGAAGUCU	1944
5277	UUAUAGAGCCGUGCUGGU	294	5277	UUAUAGAGCCGUGCUGGU	294	5295	ACCAGCACGGCUCUAUA	1945
5295	UGAGCUGCUAUAUUUUUG	295	5295	UGAGCUGCUAUAUUUUUG	295	5313	ACAAAAGUUAAGCAUUA	1946
5313	UGACUUAUAUUGCUUAC	296	5313	UGACUUAUAUUGCUUAC	296	5331	GUAAAGGAGUUAAGUGCA	1947
5331	CAGUAAUAAACUGUUGGC	297	5331	CAGUAAUAAACUGUUGGC	297	5349	GCCAAACAGUUUAUUAUCG	1948
5349	CGAGCUUGGUGAUGUCAGA	298	5349	CGAGCUUGGUGAUGUCAGA	298	5367	UCUGACAUACCAAGCUCG	1949
5367	AGAAACUAUAGCCCAUCU	299	5367	AGAAACUAUAGCCCAUCU	299	5385	AAGUUGGUCUAUAGUUUCU	1950
5385	UCUACAGCAUGCUAAUUG	300	5385	UCUACAGCAUGCUAAUUG	300	5403	CAAAUUAAGCAUGCUUAGA	1951
5403	GGAAUCUGCAAAGCGAGUU	301	5403	GGAAUCUGCAAAGCGAGUU	301	5421	AACUCGCUUUGCAGAUUCC	1952
5421	UCUUAUUGGUGUGUAAA	302	5421	UCUUAUUGGUGUGUAAA	302	5439	UUUACACACCACAUUAAGA	1953
5439	ACAUUGGUGUACGAAACU	303	5439	ACAUUGGUGUACGAAACU	303	5457	AGUUUCUGACCACAAUUG	1954
5457	UACUACGUAACGGGUGUA	304	5457	UACUACGUAACGGGUGUA	304	5475	UAGACCCGUAUAGGUAGUA	1955
5475	AGAAGCUGUGAUGUAUUG	305	5475	AGAAGCUGUGAUGUAUUG	305	5493	CAUAUACAUACACAGCUUCU	1956
5493	GGGUACUCUAUCUUUAUGAU	306	5493	GGGUACUCUAUCUUUAUGAU	306	5511	AUCAUAAAGUAUAGUAUACC	1957
5511	UAUCUUAAGACAGGUGUU	307	5511	UAUCUUAAGACAGGUGUU	307	5529	AACACCUGUCUUUAAGAUUA	1958
5529	UUCUUAUUGUGUGUGU	308	5529	UUCUUAUUGUGUGUGU	308	5547	ACACACAUUGAAUUGGAA	1959
5547	UGGUGUGAUGCUACACAA	309	5547	UGGUGUGAUGCUACACAA	309	5565	UUGUGUAGCAUACAGCACC	1960
5565	AUAUCUAGUAACAACAGAG	310	5565	AUAUCUAGUAACAACAGAG	310	5583	CUCUUGUUGUAUAGAUUAU	1961
5583	GUCUUCUUUUUGUAUGAU	311	5583	GUCUUCUUUUUGUAUGAU	311	5601	CAUCAUAAACAAAGAAAGAC	1962
5601	GUCUGACCAACCGUCUGAG	312	5601	GUCUGACCAACCGUCUGAG	312	5619	CUCAGCAGGUGGUGCAGAC	1963
5619	GUUAUUAUACAGCAAGGU	313	5619	GUUAUUAUACAGCAAGGU	313	5637	ACCUUGCUGUAUUAUUAUAC	1964
5637	UACAUUCUUAUUGUGCGAAU	314	5637	UACAUUCUUAUUGUGCGAAU	314	5655	AUUCGCACAUAAAGAAUUA	1965
5655	UGAGUACACUGGUAACUUAU	315	5655	UGAGUACACUGGUAACUUAU	315	5673	AUAGUUACCAGUGUAUCUA	1966
5673	UCAGUGUGGUCAUUAACU	316	5673	UCAGUGUGGUCAUUAACU	316	5691	AGUGUAAUGACCACACUGA	1967
5691	UCAUAUAACUGCUAAGGAG	317	5691	UCAUAUAACUGCUAAGGAG	317	5709	CUCUUAAGCAGUUAUUAUGA	1968
5709	GACCCUCUAUCGUUAUUGAC	318	5709	GACCCUCUAUCGUUAUUGAC	318	5727	GUCAAAUACGAUAGAGGUGUC	1969
5727	CGGAGCUCACCUUACAAAG	319	5727	CGGAGCUCACCUUACAAAG	319	5745	CUUUGUAAGGUGAGCUCUCCG	1970
5745	GAUGUCAGAGUAACAAGGA	320	5745	GAUGUCAGAGUAACAAGGA	320	5763	UCCUUUGUACUCUGACUAC	1971
5763	ACCAGUGACUGAUUUUUC	321	5763	ACCAGUGACUGAUUUUUC	321	5781	GAAAACAUACAGUCACUGGU	1972
5781	CUACAAGGAAACAUUUUAC	322	5781	CUACAAGGAAACAUUUUAC	322	5799	GUAGAUGUUUCCUUGUAG	1973
5799	CACUACAACCAUUAAGCCU	323	5799	CACUACAACCAUUAAGCCU	323	5817	AGGCUUGAUGGUUUGUAGUG	1974
5817	UGUGUCGUUAUAAACUCGAU	324	5817	UGUGUCGUUAUAAACUCGAU	324	5835	AUCGAGUUUAUACGACACA	1975
5835	UGGAGUUACUUAACACAGAG	325	5835	UGGAGUUACUUAACACAGAG	325	5853	CUCUGUGUAAGUAACUCCA	1976
5853	GAUUGAACCAAAAUUGGAU	326	5853	GAUUGAACCAAAAUUGGAU	326	5871	AUCCAAUUUUUGGUUCAAUC	1977
5871	UGGGUUAUUUAUAAAAGGAU	327	5871	UGGGUUAUUUAUAAAAGGAU	327	5889	AUCCUUUUUUUAUAAUACCCA	1978
5889	UAUUGCUUAUUAUACAGAG	328	5889	UAUUGCUUAUUAUACAGAG	328	5907	CUCUGUAUAGUAAGCAUUA	1979
5907	GCAGCCUUAUAGACCUUUGUA	329	5907	GCAGCCUUAUAGACCUUUGUA	329	5925	UACAAGGUCUAUAGGCUUGC	1980
5925	ACCAACUCACCAUUAACCA	330	5925	ACCAACUCACCAUUAACCA	330	5943	UGGUAAUUGGUUAGUUGGU	1981

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5943	AAUUGCGAGUUUUGAUAAU	331	5943	AAUUGCGAGUUUUGAUAAU	331	5961	AUUAUCAAACUUGCAUUU	1982
5961	UUUCAAACUACAUUGUUCU	332	5961	UUUCAAACUACAUUGUUCU	332	5979	AGAACAUGUGAGUUUGAAA	1983
5979	UAACACAAAUUUGCUGAU	333	5979	UAACACAAAUUUGCUGAU	333	5997	AUCAGCAAAUUUGUGUUA	1984
5997	UGAUUUAAAUCAAAUUGACA	334	5997	UGAUUUAAAUCAAAUUGACA	334	6015	UGCAUUUUAUUUAAAUA	1985
6015	AGGUUUCACAAAGCCAGCU	335	6015	AGGUUUCACAAAGCCAGCU	335	6033	AGCUGGUUUUGUAGGCCU	1986
6033	UUCACGAGAGCUUUCUGUC	336	6033	UUCACGAGAGCUUUCUGUC	336	6051	GACAGUAGCUCUGUGAA	1987
6051	CACAUUCUCCAGACUUG	337	6051	CACAUUCUCCAGACUUG	337	6069	CAAGUCUGGGAAGAAUGUG	1988
6069	GAAUGGCGAUGUAGUGGCU	338	6069	GAAUGGCGAUGUAGUGGCU	338	6087	AGCCACUACUCCGCAUUC	1989
6087	UAUUGACUAUAGACACUAU	339	6087	UAUUGACUAUAGACACUAU	339	6105	AUAGUGUCUAUAGUCAUA	1990
6105	UUCAGCGAGUUUCAAAGAA	340	6105	UUCAGCGAGUUUCAAAGAA	340	6123	UUUCUUGAAACUUGCUGAA	1991
6123	AGGUGCUAAUUAUUGGCAC	341	6123	AGGUGCUAAUUAUUGGCAC	341	6141	AUGCAGUAAUUUAGCACC	1992
6141	UAAGCCAAUUGUUGGCAC	342	6141	UAAGCCAAUUGUUGGCAC	342	6159	GUGCCAAACAAUUGGCUA	1993
6159	CAUUAACCCAGGCUACAACC	343	6159	CAUUAACCCAGGCUACAACC	343	6177	GGUUGAGCCUGGUUAAUG	1994
6177	CAAGACAACGUUCAAACCA	344	6177	CAAGACAACGUUCAAACCA	344	6195	UGGUUUGAACGUUGUCUUG	1995
6195	AAACAUUGGUGUUUACGU	345	6195	AAACAUUGGUGUUUACGU	345	6213	ACGUAAACACCAAGUGUUU	1996
6213	UUUGCUUUGGAGUACAAG	346	6213	UUUGCUUUGGAGUACAAG	346	6231	CUUUGUACUCCAAAGACAA	1997
6231	GCCAGUAGAUACUCAAU	347	6231	GCCAGUAGAUACUCAAU	347	6249	AUUUGAAUUAUACUUGGC	1998
6249	UUCAUUUGAAGUUCUGGCA	348	6249	UUCAUUUGAAGUUCUGGCA	348	6267	UGCCAGAACUUCAAUUGAA	1999
6267	AGUAGAACACACAAAGGA	349	6267	AGUAGAACACACAAAGGA	349	6285	UCCUUGUGUGUCUUCUACU	2000
6285	AAUGGACAAUUGCUUGU	350	6285	AAUGGACAAUUGCUUGU	350	6303	ACAAGCAAGUUGUCCAUU	2001
6303	UGAAAGUACAACCCACC	351	6303	UGAAAGUACAACCCACC	351	6321	GGUGGUUGUUGACUUA	2002
6321	CUCUGAAGAGUAGUGGAA	352	6321	CUCUGAAGAGUAGUGGAA	352	6339	UCCACUACUUCUUCAGAG	2003
6339	AAAUCCUACCAUACAGAG	353	6339	AAAUCCUACCAUACAGAG	353	6357	CUUCUGUUGUAGGAAUUA	2004
6357	GGAAGUCAUAGAGUGAC	354	6357	GGAAGUCAUAGAGUGAC	354	6375	GUCACACUUAUGACUUC	2005
6375	CGUGAAACUACCCGAAGU	355	6375	CGUGAAACUACCCGAAGU	355	6393	AACUUGGUUUAUUCACG	2006
6393	UGUAGGCAUUGUCAUACU	356	6393	UGUAGGCAUUGUCAUACU	356	6411	AAGUAGACAUUGCCUACA	2007
6411	UAAACCAUCAGUAGAGGU	357	6411	UAAACCAUCAGUAGAGGU	357	6429	ACCUCAUCUGUAGGUUUA	2008
6429	UGUAAAGUAACAAAGAG	358	6429	UGUAAAGUAACAAAGAG	358	6447	CUCUUGUUAUUAUAACA	2009
6447	GUUAGGUCAUGAGAUUU	359	6447	GUUAGGUCAUGAGAUUU	359	6465	AAGAUCUACUAGCCUAA	2010
6465	UAUGGUGUUAUUGUGGAA	360	6465	UAUGGUGUUAUUGUGGAA	360	6483	UCCACAUAAAGCAGCCUA	2011
6483	AAACACAAGCAUUAACAU	361	6483	AAACACAAGCAUUAACAU	361	6501	AAUGGUAAUGCUUGUUA	2012
6501	UAGAAACCAUUAUGAGCU	362	6501	UAGAAACCAUUAUGAGCU	362	6519	AAGCUCAUUAAGGUUUA	2013
6519	UUCACUAGCCUUAAGGUUA	363	6519	UUCACUAGCCUUAAGGUUA	363	6537	UAAACCUAAGGCUAGUGAA	2014
6537	AAAAACAUIUGCCACUUA	364	6537	AAAAACAUIUGCCACUUA	364	6555	AUGAGUGGCAUUAUUAUU	2015
6555	UGGUUUGGUGGCAUUAU	365	6555	UGGUUUGGUGGCAUUAU	365	6573	AUUAUUGCAGCAUUAJCCA	2016
6573	UAGUUGUCCUUGGAGUAA	366	6573	UAGUUGUCCUUGGAGUAA	366	6591	UUUACUCCAAAGGACACUA	2017
6591	AUUUUGGUUUAUUGUCAA	367	6591	AUUUUGGUUUAUUGUCAA	367	6609	UUUGCAUUAAGCCAAAUU	2018
6609	ACCAUUCUUAAGGACAAGCA	368	6609	ACCAUUCUUAAGGACAAGCA	368	6627	UCCUUGUCCUUAAGAAUGGU	2019
6627	AGCAUUUAACAACAUAUAAU	369	6627	AGCAUUUAACAACAUAUAAU	369	6645	AUUUGAUUGUUAUUAUGCU	2020
6645	UUGCGCUAAGAGAUUAAGCA	370	6645	UUGCGCUAAGAGAUUAAGCA	370	6663	UGCUAAUCUCUUAAGCGCAA	2021
6663	ACAACGUGUGUUUAACAUA	371	6663	ACAACGUGUGUUUAACAUA	371	6681	AUUGUUAACACACACGUUGU	2022
6681	UUUAUAGCCUUAUGUGUUU	372	6681	UUUAUAGCCUUAUGUGUUU	372	6699	AAACACAUAAAGGCAUUA	2023

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6699	UACAUUUAUUGUCCAAUUG	373	6699	UACAUUUAUUGUCCAAUUG	373	6717	CAUUUGGAACAAUUAUUGA	2024
6717	GUGUACUUUUUACUAAAAGU	374	6717	GUGUACUUUUUACUAAAAGU	374	6735	ACUUUUUAGUAAAAGUACAC	2025
6735	UACCAUUUCUAGAAUUAAGA	375	6735	UACCAUUUCUAGAAUUAAGA	375	6753	UCUAAUUUCUAGAAUUGGUA	2026
6753	AGCUACACUACCUAACACU	376	6753	AGCUACACUACCUAACACU	376	6771	AGUUGUAGGUAGUGAAGCU	2027
6771	UAUUGCUAAAAUAGUGUU	377	6771	UAUUGCUAAAAUAGUGUU	377	6789	AACACUAAUUUUUAGCAUUA	2028
6789	UAAGAGUGUUGCUAAAUA	378	6789	UAAGAGUGUUGCUAAAUA	378	6807	UAUUUUAGCAACACUCUUA	2029
6807	AUGUUUGGAUGCCGGCAUU	379	6807	AUGUUUGGAUGCCGGCAUU	379	6825	AUUGCCGGCAUCCAAACAU	2030
6825	UAUUUAUGUGAAGUACGCC	380	6825	UAUUUAUGUGAAGUACGCC	380	6843	GGUGACUUCACCAUAAUUA	2031
6843	CAAAUUUUUUAUUUUGUUC	381	6843	CAAAUUUUUUAUUUUGUUC	381	6861	GAACAUUUJAGAAAUUUG	2032
6861	CACAAUCGCUAUGUGGCUA	382	6861	CACAAUCGCUAUGUGGCUA	382	6879	UAGCCACAUAGCGAUUGUG	2033
6879	AUUGUUGUUAAGUAAUUGC	383	6879	AUUGUUGUUAAGUAAUUGC	383	6897	GCAAAUACUUAACAAACAU	2034
6897	CUUAGGUUCUCUAAUCUGU	384	6897	CUUAGGUUCUCUAAUCUGU	384	6915	ACAGAUUAGAGAACCCUAG	2035
6915	UGUAACUGCGCUUUUGGU	385	6915	UGUAACUGCGCUUUUGGU	385	6933	ACCAAAAGCAGCAGUUAACA	2036
6933	UGUACUCUUAUCUAAUUUU	386	6933	UGUACUCUUAUCUAAUUUU	386	6951	AAAUUJAGUUAAGAGUACA	2037
6951	UGGUGCUCUUCUUAUUGU	387	6951	UGGUGCUCUUCUUAUUGU	387	6969	ACAAUJAGAAAGAGACCCA	2038
6969	UAUUGGCGUUAAGAAUUG	388	6969	UAUUGGCGUUAAGAAUUG	388	6987	CAUUCUCUUAACGCCAUUA	2039
6987	GUACUUAUUUAGGCUAAC	389	6987	GUACUUAUUUAGGCUAAC	389	7005	GUUAGACGAUUUAAGAUAC	2040
7005	CGUUAUCUUAUGGAAUUC	390	7005	CGUUAUCUUAUGGAAUUC	390	7023	GAUUCUUAUAGUUAACG	2041
7023	CUGUAGGCUUUCUUUCCU	391	7023	CUGUAGGCUUUCUUUCCU	391	7041	AGGAAAGAACCUUACACAG	2042
7041	UUGCAGCAUUUUAUAGU	392	7041	UUGCAGCAUUUUAUAGU	392	7059	ACUUAACAAUUGCUGCAA	2043
7059	UGGAUUAGACUCCCUUGAU	393	7059	UGGAUUAGACUCCCUUGAU	393	7077	AUCAAGGGAGUCUUAUCCA	2044
7077	UUCUUAUCCAGCUCUUGAA	394	7077	UUCUUAUCCAGCUCUUGAA	394	7095	UUCAAAGAGCUGGAUAAAGAA	2045
7095	AACCAUUCAGGUGACGAUU	395	7095	AACCAUUCAGGUGACGAUU	395	7113	AUCGUCACCUGAAUGGUU	2046
7113	UUCAGCUAACAGCUAGAC	396	7113	UUCAGCUAACAGCUAGAC	396	7131	GUCUAGCUUUGUACGAUGAA	2047
7131	CUUGACAAUUUJAGGUCUG	397	7131	CUUGACAAUUUJAGGUCUG	397	7149	CAGACCUAAAUUGUCAAG	2048
7149	GGCCGCUAGUGGGUUUUG	398	7149	GGCCGCUAGUGGGUUUUG	398	7167	CAAAACCCACUCAGCGGCC	2049
7167	GGCAUUAUUGUUGUUCACA	399	7167	GGCAUUAUUGUUGUUCACA	399	7185	UGUGAACCAUUAUUGCC	2050
7185	AAAAUUCUUUUUAUUUA	400	7185	AAAAUUCUUUUUAUUUA	400	7203	UAAUAAAUAAGAAUUUU	2051
7203	AGGUCUUAUCAGCUAAUUG	401	7203	AGGUCUUAUCAGCUAAUUG	401	7221	CAUUUAUAGCUGAAAGACCU	2052
7221	GCAGGUGUUCUUGGCUAU	402	7221	GCAGGUGUUCUUGGCUAU	402	7239	AUAGCCAAAGAACACCCUGC	2053
7239	UUUUGCUAGUCAUUUCAUC	403	7239	UUUUGCUAGUCAUUUCAUC	403	7257	GAUGAAUUGACUAGCAAAA	2054
7257	CAGCAUUCUUGGCUAUG	404	7257	CAGCAUUCUUGGCUAUG	404	7275	CAGUAGCCAAAGAAUUGCUG	2055
7275	GUGUUUAUAGUUAUUAU	405	7275	GUGUUUAUAGUUAUUAU	405	7293	AAUACUAAUGAUAAACCAC	2056
7293	UGUACAAUUGGCCCGGUU	406	7293	UGUACAAUUGGCCCGGUU	406	7311	AACGGGUGCCAUUUGUACA	2057
7311	UUCUGCAAUGGUUAGGAUG	407	7311	UUCUGCAAUGGUUAGGAUG	407	7329	CAUCCUAAACCAUUGCAGAA	2058
7329	GUACAUCUUCUUUGCUUCU	408	7329	GUACAUCUUCUUUGCUUCU	408	7347	AGAAGCAAGAAAGAUUAC	2059
7347	UUUCUACUACAUUUGGAAG	409	7347	UUUCUACUACAUUUGGAAG	409	7365	CUUCCAUUUGUAGUAGAA	2060
7365	GAGCUAUGUUAUUAUUAUG	410	7365	GAGCUAUGUUAUUAUUAUG	410	7383	CAUGAUUAGAAUUAAGCUC	2061
7383	GGAUGGUUGCACCUCUUCG	411	7383	GGAUGGUUGCACCUCUUCG	411	7401	CGAAGAGGUGCAACCAUCC	2062
7401	GACUUGCAUGAUGUGCUAU	412	7401	GACUUGCAUGAUGUGCUAU	412	7419	AUAGCACAUCAUGCAAGUC	2063
7419	UAAGCGCAUUGUGGCCACA	413	7419	UAAGCGCAUUGUGGCCACA	413	7437	UGUGGCACGAUUGCGCUUA	2064
7437	ACGCGUUGAGUGUACACU	414	7437	ACGCGUUGAGUGUACACU	414	7455	AGUUGUACACUACACGCGU	2065

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7455	UAUUGUUAUUGGCAUGAAG	415	7455	UAUUGUUAUUGGCAUGAAG	415	7473	CUUCAUGCCAUUAACAAUA	2066
7473	GAGAUUUUUAUUGUUAU	416	7473	GAGAUUUUUAUUGUUAU	416	7491	AUAGACAUAGAAAGAUUC	2067
7491	UGCAAUUGGAGCGGUGGC	417	7491	UGCAAUUGGAGCGGUGGC	417	7509	GCCACGGCCUCCAUUUGCA	2068
7509	CUUCUGCAAGACUCACAAU	418	7509	CUUCUGCAAGACUCACAAU	418	7527	AUUGUGAGUCUUGCAGAA	2069
7527	UUGGAUUUGUCUAAUUGU	419	7527	UUGGAUUUGUCUAAUUGU	419	7545	ACAAUUGAGACAAUCCAA	2070
7545	UGACACAUUUUGCAGUGGU	420	7545	UGACACAUUUUGCAGUGGU	420	7563	ACCAGUGCAAAUUGUGCA	2071
7563	UAGUACAUUUAUAGUGAU	421	7563	UAGUACAUUUAUAGUGAU	421	7581	AUCACUAAUAGAUUACUA	2072
7581	UGAAGUUGCUGUGAUUUG	422	7581	UGAAGUUGCUGUGAUUUG	422	7599	CAAAUCACGAGCAACUUA	2073
7599	GUCACUCCAGUUAAAAGA	423	7599	GUCACUCCAGUUAAAAGA	423	7617	UCUUUUAACUGGAGUGAC	2074
7617	ACCAUUCACCCUACUGAC	424	7617	ACCAUUCACCCUACUGAC	424	7635	GUCAGUAGGUUGAUUGGU	2075
7635	CCAGUCAUCGUUAUUGUU	425	7635	CCAGUCAUCGUUAUUGUU	425	7653	AACAAUUAACGAGACUGG	2076
7653	UGAUGUGUUGCUGUGAAA	426	7653	UGAUGUGUUGCUGUGAAA	426	7671	UUUCACAGCAACAUUAUA	2077
7671	AAUUGGCGGCUUACCCUC	427	7671	AAUUGGCGGCUUACCCUC	427	7689	GAGUGAAGCGCGCCAUUU	2078
7689	CUACUUGACAGGUGUGU	428	7689	CUACUUGACAGGUGUGU	428	7707	ACCAGCCUUGUCAAAUAG	2079
7707	UCAAAGACCUUAGAGAGA	429	7707	UCAAAGACCUUAGAGAGA	429	7725	UCUCUUAAGGUUUUUGA	2080
7725	ACAUCCGCUUCCAUUUU	430	7725	ACAUCCGCUUCCAUUUU	430	7743	AAAUGGGAGAGCGGAUGU	2081
7743	UGUCAAUUUAGACAAUUG	431	7743	UGUCAAUUUAGACAAUUG	431	7761	CAAAUUGUCUAAAUGACA	2082
7761	GAGACUUAACACUAAUA	432	7761	GAGACUUAACACUAAUA	432	7779	UUUAGUGUUGUAGCUCUC	2083
7779	AGGUUACUUGCCUUAUUA	433	7779	AGGUUACUUGCCUUAUUA	433	7797	AUUAUUAAGGAGUGAAACCU	2084
7797	UGUCAUAGUUUUGAUGGC	434	7797	UGUCAUAGUUUUGAUGGC	434	7815	GCCAUCAAAACUUAUGACA	2085
7815	CAAGUCCAAUUGCGACGAG	435	7815	CAAGUCCAAUUGCGACGAG	435	7833	CUCGUGCAUUGGACUUG	2086
7833	GUCUGCUUUAAGUGUGCU	436	7833	GUCUGCUUUAAGUGUGCU	436	7851	AGCAGACUUAAGAGCAGAC	2087
7851	UUCUGUGUACUACAGUCAG	437	7851	UUCUGUGUACUACAGUCAG	437	7869	CUGACUGUAGUACACAGAA	2088
7869	GCUGAUGUGCCAAACUUAU	438	7869	GCUGAUGUGCCAAACUUAU	438	7887	AUAGGUUGGCAUACAGC	2089
7887	UCUGUUUGCUUAGCAAGCU	439	7887	UCUGUUUGCUUAGCAAGCU	439	7905	AGCUUGGUAAGCAACAGAG	2090
7905	UCUUGUAUCAGACGUUGGA	440	7905	UCUUGUAUCAGACGUUGGA	440	7923	UCCAACGUCUGAUACAAGA	2091
7923	AGAUAGUACUAGUUUCC	441	7923	AGAUAGUACUAGUUUCC	441	7941	GGAAACUUAAGUACUUAUCU	2092
7941	CGUUAAGAUUUUUGAUGCU	442	7941	CGUUAAGAUUUUUGAUGCU	442	7959	AGCAUCAAAACUUAUACG	2093
7959	UUAUGUCGACACCUUUUCA	443	7959	UUAUGUCGACACCUUUUCA	443	7977	UGAAAAGGUGUGGACAUAA	2094
7977	AGCAACUUUUUAGUGUCCU	444	7977	AGCAACUUUUUAGUGUCCU	444	7995	AGGAACACUAAAAGUUGCU	2095
7995	UAUGGAAAACUUUAGGCA	445	7995	UAUGGAAAACUUUAGGCA	445	8013	UGCCUUAAGUUUUUCCAUUA	2096
8013	ACUUGUUGCUACAGCUCAC	446	8013	ACUUGUUGCUACAGCUCAC	446	8031	GUGAGCUGUAGCAACAAGU	2097
8031	CAGCGAGUUAGCAAAAGGU	447	8031	CAGCGAGUUAGCAAAAGGU	447	8049	ACCCUUUGCUAACUCGCGUG	2098
8049	UGUAGCUUUUAGUUGGUGUC	448	8049	UGUAGCUUUUAGUUGGUGUC	448	8067	GACACCAUCUAAAAGCUACA	2099
8067	CCUUUCUACAUUCGUGUCA	449	8067	CCUUUCUACAUUCGUGUCA	449	8085	UGACACGAAUUGUAGAAAGG	2100
8085	AGUGCCCGACAAAGGUGUU	450	8085	AGUGCCCGACAAAGGUGUU	450	8103	AACACCUUGUCGGGACGCU	2101
8103	UGUUGAUACCGGAUGUUGAC	451	8103	UGUUGAUACCGGAUGUUGAC	451	8121	GUCAACAUCGGUUAUCAACA	2102
8121	CACAAAGGAUGUUUAUUGAA	452	8121	CACAAAGGAUGUUUAUUGAA	452	8139	UUCAAUACAUCCUUGUGU	2103
8139	AUGUCUCAAACUUUACAU	453	8139	AUGUCUCAAACUUUACAU	453	8157	AUGUGAAAGUUUGAGAGAU	2104
8157	UCACUCUGACUUAGAAGUG	454	8157	UCACUCUGACUUAGAAGUG	454	8175	CACUUCUAAAGUCAGAGUGA	2105
8175	GACAGGUGACAGUUGUAAAC	455	8175	GACAGGUGACAGUUGUAAAC	455	8193	GUUACACUGUCACCUGUC	2106
8193	CAAUUUAUGCUCACCCUUAU	456	8193	CAAUUUAUGCUCACCCUUAU	456	8211	AUAGGUGAGCAUGAAAUUG	2107

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8211	UAAUAAAGGUUGAAAAACAUG	457	8211	UAAUAAAGGUUGAAAAACAUG	457	8229	CAUGUUUUUCAAACCUUAUUA	2108
8229	GACGCCAGAGAUUUUGGC	458	8229	GACGCCAGAGAUUUUGGC	458	8247	GCCAAAGUUCUGGGCGUC	2109
8247	CGCAUGAUUUGACUGUAAU	459	8247	CGCAUGAUUUGACUGUAAU	459	8265	AUUACAGUCAUAACGCG	2110
8265	UGCAAGGCAUAUCAAUGCC	460	8265	UGCAAGGCAUAUCAAUGCC	460	8283	GGCAUUGAUUGCCUUGCA	2111
8283	CCAAGUAGCAAAAAGUCAC	461	8283	CCAAGUAGCAAAAAGUCAC	461	8301	GUGACUUUUUGCUACUUGG	2112
8301	CAUUGUUUUCACUACUUGG	462	8301	CAUUGUUUUCACUACUUGG	462	8319	CCAGAUUGAGUGAAACAUUG	2113
8319	GAUUGUAAAAGACUACAUG	463	8319	GAUUGUAAAAGACUACAUG	463	8337	CAUGUAGUCUUUUACAUC	2114
8337	GUCUUUUCUGAACAGCUG	464	8337	GUCUUUUCUGAACAGCUG	464	8355	CAGCUGUUCAGAUAAAAGAC	2115
8355	GCGUAAACAAUUCGUAGU	465	8355	GCGUAAACAAUUCGUAGU	465	8373	ACUACGAUUUUGUUUACGC	2116
8373	UGCUGCCAAAGAAACAAC	466	8373	UGCUGCCAAAGAAACAAC	466	8391	GUUGUUCUUCUUGGCAGCA	2117
8391	CAUACCUUUUAGACUAAU	467	8391	CAUACCUUUUAGACUAAU	467	8409	AGUUAGUCUAAAAGGUUUG	2118
8409	UUGUGCUACAACUAGACAG	468	8409	UUGUGCUACAACUAGACAG	468	8427	CUGUCUAGUUGUAGCACAA	2119
8427	GGUUGUCAUUGUCAUAU	469	8427	GGUUGUCAUUGUCAUAU	469	8445	AGUUUAGCAUUGAGAACCC	2120
8445	UACUAAAUCUCACUCAAG	470	8445	UACUAAAUCUCACUCAAG	470	8463	CUUGAGUGAGAUUUUAGUA	2121
8463	GGUGGUUAGAUUUGUUAU	471	8463	GGUGGUUAGAUUUGUUAU	471	8481	ACUAAACUUCUACCAACC	2122
8481	UACUUGUUUUAACUUAU	472	8481	UACUUGUUUUAACUUAU	472	8499	CAUAAAGUUUAAACAAAG	2123
8499	GCUUAAAGGCCACAUUAU	473	8499	GCUUAAAGGCCACAUUAU	473	8517	CAUAAAGUUGGCCUUAAGC	2124
8517	GUGCGUUCUUGCUGCAUUG	474	8517	GUGCGUUCUUGCUGCAUUG	474	8535	CAUUGCAGCAAGAACGCAC	2125
8535	GGUUUGUUUAUUGUUAU	475	8535	GGUUUGUUUAUUGUUAU	475	8553	CAUAAAGAUUAAACAAACC	2126
8553	GCCAGUACAUAUUGUCA	476	8553	GCCAGUACAUAUUGUCA	476	8571	UGACAAGUUAUGUACUGGC	2127
8571	AUCCAUUGUUGUUAACACA	477	8571	AUCCAUUGUUGUUAACACA	477	8589	UGUGUAAACCAUUGGGAU	2128
8589	AAUAGAAUUAUUGGUUAC	478	8589	AAUAGAAUUAUUGGUUAC	478	8607	GUAACCAUUGAUUUCAUUU	2129
8607	CAAGCCAUUUCAGGAUGGU	479	8607	CAAGCCAUUUCAGGAUGGU	479	8625	ACCAUCCUGAAUGGCUUUG	2130
8625	UUCACUCUGAGCAUAU	480	8625	UUCACUCUGAGCAUAU	480	8643	AUUGAUUCACGAGAGACA	2131
8643	UUCUACUGAGAUUUUU	481	8643	UUCUACUGAGAUUUUU	481	8661	AAAACAUAUCAGUAGAA	2132
8661	UGCAAAUAAACAUGCUGGU	482	8661	UGCAAAUAAACAUGCUGGU	482	8679	ACCAGCAUGUUUUAUUUGCA	2133
8679	UUUUGACGCAUGGUUUAAGC	483	8679	UUUUGACGCAUGGUUUAAGC	483	8697	GCUAAACCAUGCGUACAAA	2134
8697	CCAGCGUGGUUUUUAUAC	484	8697	CCAGCGUGGUUUUUAUAC	484	8715	GUAUGAACCAACACGCUGG	2135
8715	CAAAAUGACAAAAGCUGC	485	8715	CAAAAUGACAAAAGCUGC	485	8733	GCAGCUUUUGUCAUUUUUG	2136
8733	CCUUGUAGUAGCUUAUC	486	8733	CCUUGUAGUAGCUUAUC	486	8751	GAUAGCAGCUACUACAGGG	2137
8751	CAUUAACAAGAGAUUUGGU	487	8751	CAUUAACAAGAGAUUUGGU	487	8769	ACCAUUCUCUUGUUAUUG	2138
8769	UUUCAUAGUGCCUGGCUUA	488	8769	UUUCAUAGUGCCUGGCUUA	488	8787	UAAGCCAGGCACUUAUGAAA	2139
8787	ACCGGUUACUUGUGUGAGA	489	8787	ACCGGUUACUUGUGUGAGA	489	8805	UCUCAGCAGUACCCCGGU	2140
8805	AGCAUAUUAUGGUGACUUC	490	8805	AGCAUAUUAUGGUGACUUC	490	8823	GAUGUACCAUUGAUUGCU	2141
8823	CUUGCAUUUUCUACCCUCU	491	8823	CUUGCAUUUUCUACCCUCU	491	8841	ACGAGGUAGAAAUGCAAG	2142
8841	UGUUUUUAGUGUGUUGGC	492	8841	UGUUUUUAGUGUGUUGGC	492	8859	GCCAAACAGCAUAAAACA	2143
8859	CAACAUIUGCUACACACCU	493	8859	CAACAUIUGCUACACACCU	493	8877	AGGUGUGUAGCAAAUGUUG	2144
8877	UUCCAAACUUAUUGAGUAU	494	8877	UUCCAAACUUAUUGAGUAU	494	8895	AUACUCAUUGAGUUUGGAA	2145
8895	UAGUGAUUUUGCUACCCUCU	495	8895	UAGUGAUUUUGCUACCCUCU	495	8913	AGAGGUAGCAAAUUCACUA	2146
8913	UGCUUGCGUUCUUGCUGCU	496	8913	UGCUUGCGUUCUUGCUGCU	496	8931	AGCAGCAAGAACGCAAGCA	2147
8931	UGAGUGUACAUAUUUUUAAG	497	8931	UGAGUGUACAUAUUUUUAAG	497	8949	CUUAAAAUUUGUACACUCA	2148
8949	GGAUGCUAUGGGCAAAACCU	498	8949	GGAUGCUAUGGGCAAAACCU	498	8967	AGGUUUGCCCAUAGCAUCC	2149

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8967	UGGCCAAUUAUUAUGAC	499	8967	UGGCCAAUUAUUAUGAC	499	8985	GUCAUAAACAAUUAUGGACA	2150
8985	CACUAAUUAUUAUGAGGGU	500	8985	CACUAAUUAUUAUGAGGGU	500	9003	ACCCUCUAGCAAUUAUGUG	2151
9003	UUCUAAUUAUUAUGAG	501	9003	UUCUAAUUAUUAUGAG	501	9021	CUCACUAUAAAGAAUAGAA	2152
9021	GCUUGGUCAGACACUGG	502	9021	GCUUGGUCAGACACUGG	502	9039	ACGAGUGUCUGGACGAGC	2153
9039	UUAUGUGCUUAUGGAGGU	503	9039	UUAUGUGCUUAUGGAGGU	503	9057	ACCAUCCAAUAGACACAUAA	2154
9057	UUAUUAUUAUUAUGGAGGU	504	9057	UUAUUAUUAUUAUGGAGGU	504	9075	AGAAACUGUAUUAUGGAA	2155
9075	UUAUUAUUAUUAUGGAGGU	505	9075	UUAUUAUUAUUAUGGAGGU	505	9093	ACCCUCCAGGUAUUAUGGUA	2156
9093	UUCUGUUAUUAUGAGUAACA	506	9093	UUCUGUUAUUAUGAGUAACA	506	9111	UGUUAUUAUUAUUAUGAGUA	2157
9111	AACUUAUUAUUAUGAGUAACA	507	9111	AACUUAUUAUUAUGAGUAACA	507	9129	GUACUCAGCAUUAUUAUGAGUA	2158
9129	CUGUAGACAUUAUGAGUAACA	508	9129	CUGUAGACAUUAUGAGUAACA	508	9147	GCAUGUACCAUUAUUAUGAGUA	2159
9147	CGAAAGGUCAGAGUAAGGU	509	9147	CGAAAGGUCAGAGUAAGGU	509	9165	ACCUUUAUUAUUAUGAGUA	2160
9165	UUAUUAUUAUUAUGAGUAACA	510	9165	UUAUUAUUAUUAUGAGUAACA	510	9183	ACUUGUAGUAUUAUGAGUA	2161
9183	UGGUAUUAUUAUGAGUAACA	511	9183	UGGUAUUAUUAUGAGUAACA	511	9201	AUIAAGAACCAUUAUUAUGAGUA	2162
9201	UUAUUAUUAUUAUGAGUAACA	512	9201	UUAUUAUUAUUAUGAGUAACA	512	9219	AGCUCUGUAUUAUUAUGAGUA	2163
9219	UUAUUAUUAUUAUGAGUAACA	513	9219	UUAUUAUUAUUAUGAGUAACA	513	9237	ACAGAAACUUAUUAUGAGUA	2164
9237	UGGUAUUAUUAUGAGUAACA	514	9237	UGGUAUUAUUAUGAGUAACA	514	9255	AUIUAUUAUUAUUAUGAGUA	2165
9255	UUAUUAUUAUUAUGAGUAACA	515	9255	UUAUUAUUAUUAUGAGUAACA	515	9273	AAAGUUAUUAUUAUGAGUA	2166
9273	UUAUUAUUAUUAUGAGUAACA	516	9273	UUAUUAUUAUUAUGAGUAACA	516	9291	AGGUUUAUUAUUAUGAGUA	2167
9291	UGGUAUUAUUAUGAGUAACA	517	9291	UGGUAUUAUUAUGAGUAACA	517	9309	CACUUAUUAUUAUGAGUA	2168
9309	GUUUAUUAUUAUGAGUAACA	518	9309	GUUUAUUAUUAUGAGUAACA	518	9327	AGCCACUUAUUAUGAGUA	2169
9327	UGGUAUUAUUAUGAGUAACA	519	9327	UGGUAUUAUUAUGAGUAACA	519	9345	UAUUGGCAUUAUUAUGAGUA	2170
9345	AUUGGUAUUAUUAUGAGUAACA	520	9345	AUUGGUAUUAUUAUGAGUAACA	520	9363	GGCAGCAUUAUUAUGAGUA	2171
9363	CUUAUUAUUAUUAUGAGUAACA	521	9363	CUUAUUAUUAUUAUGAGUAACA	521	9381	GAUUAUUAUUAUGAGUA	2172
9381	CAGACGUAUUAUUAUGAGUAACA	522	9381	CAGACGUAUUAUUAUGAGUAACA	522	9399	CUCACCAUUAUUAUGAGUA	2173
9399	GUUAUUAUUAUUAUGAGUAACA	523	9399	GUUAUUAUUAUUAUGAGUAACA	523	9417	AGCAUUAUUAUUAUGAGUA	2174
9417	UGUAUUAUUAUUAUGAGUAACA	524	9417	UGUAUUAUUAUUAUGAGUAACA	524	9435	AAACAAUUAUUAUGAGUA	2175
9435	UUUAUUAUUAUUAUGAGUAACA	525	9435	UUUAUUAUUAUUAUGAGUAACA	525	9453	UAUUAUUAUUAUGAGUA	2176
9453	ACUUAUUAUUAUGAGUAACA	526	9453	ACUUAUUAUUAUGAGUAACA	526	9471	AGCUGUAUUAUUAUGAGUA	2177
9471	UUAUUAUUAUUAUGAGUAACA	527	9471	UUAUUAUUAUUAUGAGUAACA	527	9489	UCCCGGCAUUAUUAUGAGUA	2178
9489	AGUUAUUAUUAUGAGUAACA	528	9489	AGUUAUUAUUAUGAGUAACA	528	9507	GUAAAGACUUAUUAUGAGUA	2179
9507	CUUAUUAUUAUGAGUAACA	529	9507	CUUAUUAUUAUGAGUAACA	529	9525	AUUAUUAUUAUGAGUA	2180
9525	UUUAUUAUUAUGAGUAACA	530	9525	UUUAUUAUUAUGAGUAACA	530	9543	UGAAUUAUUAUGAGUA	2181
9543	AUUAUUAUUAUGAGUAACA	531	9543	AUUAUUAUUAUGAGUAACA	531	9561	UUGAAGUUAUUAUGAGUA	2182
9561	UUGUAUUAUUAUGAGUAACA	532	9561	UUGUAUUAUUAUGAGUAACA	532	9579	AGAAUUAUUAUGAGUA	2183
9579	UUAUUAUUAUUAUGAGUAACA	533	9579	UUAUUAUUAUUAUGAGUAACA	533	9597	CCAAUUAUUAUGAGUA	2184
9597	GAUAUUAUUAUGAGUAACA	534	9597	GAUAUUAUUAUGAGUAACA	534	9615	UUAUUAUUAUGAGUA	2185
9615	AUUAUUAUUAUGAGUAACA	535	9615	AUUAUUAUUAUGAGUAACA	535	9633	CUUAUUAUUAUGAGUA	2186
9633	GCACUUAUUAUGAGUAACA	536	9633	GCACUUAUUAUGAGUAACA	536	9651	AAAGAAUUAUUAUGAGUA	2187
9651	UUAUUAUUAUUAUGAGUAACA	537	9651	UUAUUAUUAUUAUGAGUAACA	537	9669	UUUAUUAUUAUGAGUA	2188
9669	AAGUAUUAUUAUGAGUAACA	538	9669	AAGUAUUAUUAUGAGUAACA	538	9687	UCCAUUAUUAUGAGUA	2189
9687	AGUAUUAUUAUGAGUAACA	539	9687	AGUAUUAUUAUGAGUAACA	539	9705	GAAGUAUUAUUAUGAGUA	2190
9705	CGAGGUAUUAUGAGUAACA	540	9705	CGAGGUAUUAUGAGUAACA	540	9723	ACAAUUAUUAUGAGUA	2191

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9723	UACCUUUUUGCUCAACAAG	541	9723	UACCUUUUUGCUCAACAAG	541	9741	CUUGUUGAGCAAAAAGGUA	2192
9741	GGAAUUGUACCUAAAAUUG	542	9741	GGAAUUGUACCUAAAAUUG	542	9759	CAUUUUUAGGUACAUUCC	2193
9759	GCGUAGCGAGACACUGUUG	543	9759	GCGUAGCGAGACACUGUUG	543	9777	CAACGUGUCGCUACGC	2194
9777	GCCACUACACAGUAUAAC	544	9777	GCCACUACACAGUAUAAC	544	9795	GUUAUCUGUGUAAGUGGC	2195
9795	CAGGAUCUUGCUCUAU	545	9795	CAGGAUCUUGCUCUAU	545	9813	AUAAGAGCAAGAUACCUUG	2196
9813	UAACAAGUACAAGUAUUC	546	9813	UAACAAGUACAAGUAUUC	546	9831	GAUAUACUUGACUUGUA	2197
9831	CAGUGGAGCCUUAAGUAU	547	9831	CAGUGGAGCCUUAAGUAU	547	9849	AGUAUCUAAAGGUCCACUG	2198
9849	UACCAAGCUAUCGUAAGCA	548	9849	UACCAAGCUAUCGUAAGCA	548	9867	UGCUUCACGAUAGCUGGUA	2199
9867	AGCUUGCUGCCACUUAAGCA	549	9867	AGCUUGCUGCCACUUAAGCA	549	9885	UGCUAAGUGGCAGCAAGCU	2200
9885	AAAGGCUCUAAAUAGACU	550	9885	AAAGGCUCUAAAUAGACU	550	9903	AAAGUCAUUUAGAGCCUU	2201
9903	UAGCAACUCAGGUGCUGAU	551	9903	UAGCAACUCAGGUGCUGAU	551	9921	AUCAGCACCGUAGUUGCUA	2202
9921	UGUUCUCUACCAACACCA	552	9921	UGUUCUCUACCAACACCA	552	9939	UGUGGUUGUAGAGAACA	2203
9939	ACAGCAUCAUACACUUCU	553	9939	ACAGCAUCAUACACUUCU	553	9957	AGAAGUGAUUGAUUGUCUGU	2204
9957	UGCUGUUCUGCAGAGUGGU	554	9957	UGCUGUUCUGCAGAGUGGU	554	9975	ACCACUCUGCAGAACAGCA	2205
9975	UUUAGGAAAAUUGCAUUC	555	9975	UUUAGGAAAAUUGCAUUC	555	9993	GAUAGCCAUUUUCCUAAA	2206
9993	CCGUCAGGCAAGUUGAA	556	9993	CCGUCAGGCAAGUUGAA	556	10011	UUAACUUGCCUGACGGG	2207
10011	AGGUGCAUGGUACAAGUA	557	10011	AGGUGCAUGGUACAAGUA	557	10029	UACUUGUACCAUGCACCCU	2208
10029	AACUUGGGAACUACAACU	558	10029	AACUUGGGAACUACAACU	558	10047	AGUUGUAGUCCACAGGU	2209
10047	UCUUAUUGGAUUGGUGU	559	10047	UCUUAUUGGAUUGGUGU	559	10065	CAACACAAUCCAUUAGA	2210
10065	GGAUGACACAGUAUACUGU	560	10065	GGAUGACACAGUAUACUGU	560	10083	ACAGUAUACUGUACUCC	2211
10083	UCCAAGACAGUACUUGC	561	10083	UCCAAGACAGUACUUGC	561	10101	GCAAAUGACUUGCUUGGA	2212
10101	CACAGACAGACAGUUCU	562	10101	CACAGACAGACAGUUCU	562	10119	AAGCAUGUCUUGCUGUG	2213
10119	UAUCCUAACUAUGAAGAU	563	10119	UAUCCUAACUAUGAAGAU	563	10137	AUCUUAUAGUAGGUAUA	2214
10137	UCUGCUAUUCGCAAUCC	564	10137	UCUGCUAUUCGCAAUCC	564	10155	GGAUUUGGAAUAGCAGA	2215
10155	CAACCAUAGCUUUCUUGU	565	10155	CAACCAUAGCUUUCUUGU	565	10173	AACAAGAAAGCUAUGGUUG	2216
10173	UCAGGCUAGCAUUGUCAA	566	10173	UCAGGCUAGCAUUGUCAA	566	10191	UUGAACAUUGCCAGCCUGA	2217
10191	ACUUCGUGUUAUUGGCCAU	567	10191	ACUUCGUGUUAUUGGCCAU	567	10209	AUGGCCAAUACACGAAGU	2218
10209	UUCUAUGCAAAUUGUCUG	568	10209	UUCUAUGCAAAUUGUCUG	568	10227	CAGACAAUUUGCAUAGAA	2219
10227	GCUUAGGCUUAAAGUUGAU	569	10227	GCUUAGGCUUAAAGUUGAU	569	10245	AUCAACUUAAGCCUAAAGC	2220
10245	UACUUCUAAACCUAAGACA	570	10245	UACUUCUAAACCUAAGACA	570	10263	UGUCUUAAGGUUAAGAGUA	2221
10263	ACCAAGUAUAAAUUGUC	571	10263	ACCAAGUAUAAAUUGUC	571	10281	GACAAUUUAUACUUGGU	2222
10281	CCGUUCCAAACUUGUCAA	572	10281	CCGUUCCAAACUUGUCAA	572	10299	UUGACCAGGUUGGUAACGG	2223
10299	AACAUUUUGAGUUCUAGCA	573	10299	AACAUUUUGAGUUCUAGCA	573	10317	UGCUAAGACUGAAAAUGUU	2224
10317	AUGCUACAAGGUUACACCA	574	10317	AUGCUACAAGGUUACACCA	574	10335	UGGUAACCAUUGUAGCAU	2225
10335	AUCUGGUGUUAUACAGUGU	575	10335	AUCUGGUGUUAUACAGUGU	575	10353	ACACUGAUAACACCAAGAU	2226
10353	UGCCAUGAGACCUAAUACAU	576	10353	UGCCAUGAGACCUAAUACAU	576	10371	AUGAAUAGGUCUUAUGCA	2227
10371	UACCAUUAAGGUUCUUCU	577	10371	UACCAUUAAGGUUCUUCU	577	10389	GAAGAACCUIUAUUGGUA	2228
10389	CCUUAUUGGAUUGGUGU	578	10389	CCUUAUUGGAUUGGUGU	578	10407	ACACAUGAUCCAUUAGG	2229
10407	UAGUUGGUUUAACAUU	579	10407	UAGUUGGUUUAACAUU	579	10425	AUGUUAAAAACCAACACUA	2230
10425	UGAUUAUGAUUGCGUGUCU	580	10425	UGAUUAUGAUUGCGUGUCU	580	10443	AGACACGCAUUAUAUACA	2231
10443	UUUCUGCUUAUUGCAUCAU	581	10443	UUUCUGCUUAUUGCAUCAU	581	10461	AUGAUGCAUUAAGCAGAAA	2232
10461	UAUGGAGCUUCCAAACAGGA	582	10461	UAUGGAGCUUCCAAACAGGA	582	10479	UCCUGUUGGAAGCUCCAUA	2233

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10479	AGUACACGCGUACUGAC	583	10479	AGUACACGCGUACUGAC	583	10497	GUCAGUACACGCGUGUACU	2234
10497	CUUAGAAGGUAUUCUUAU	584	10497	CUUAGAAGGUAUUCUUAU	584	10515	AUAGAUAUUCUUCUUAAG	2235
10515	UGGUCCAUUUGUUGACAGA	585	10515	UGGUCCAUUUGUUGACAGA	585	10533	UCUGUCAACAAUUGGACCA	2236
10533	ACAAACUGCACAGGUGCA	586	10533	ACAAACUGCACAGGUGCA	586	10551	UGCAGCCUGUGCAGUUGU	2237
10551	AGGUACAGACACAACCAUA	587	10551	AGGUACAGACACAACCAUA	587	10569	UAUGGUUGUGUGUGUACCU	2238
10569	AACUAUAAUUGUUGGCA	588	10569	AACUAUAAUUGUUGGCA	588	10587	UGCCAAAACAUUAAUUGU	2239
10587	AGGGCUGUAUGUUGCUUU	589	10587	AGGGCUGUAUGUUGCUUU	589	10605	AACAGACAUUACGCAU	2240
10605	UAUCAUUGGUAUAGGUGG	590	10605	UAUCAUUGGUAUAGGUGG	590	10623	CCACCUAACCAUUGUAU	2241
10623	GUUUCUAAUAGAUUACAC	591	10623	GUUUCUAAUAGAUUACAC	591	10641	GGUGAAUUAUAAAGAAC	2242
10641	CACUACUUGAAUAGCUUU	592	10641	CACUACUUGAAUAGCUUU	592	10659	AAAGUACUCAAAGUAGUG	2243
10659	UAACCUUGGCAUAGAAAG	593	10659	UAACCUUGGCAUAGAAAG	593	10677	CUUCAUUGCCACAAAGUUA	2244
10677	GUACAACUAUAGACCUUUG	594	10677	GUACAACUAUAGACCUUUG	594	10695	CAAAGGUUCAUAGUUGUAC	2245
10695	GACACAAGAUCAUUGUAGC	595	10695	GACACAAGAUCAUUGUAGC	595	10713	GUCAACAUGAUUUUGUGUC	2246
10713	CAUAUUGGACCCUUCUUCU	596	10713	CAUAUUGGACCCUUCUUCU	596	10731	AGAAAGAGGCCCAUAUUG	2247
10731	UGCUCAACAGGAUUGCC	597	10731	UGCUCAACAGGAUUGCC	597	10749	GGCAUUCUGUUGUUGAGCA	2248
10749	CGUCUUAUAGUUGUGCU	598	10749	CGUCUUAUAGUUGUGCU	598	10767	AGCACAUUUAUUAAGACG	2249
10767	UGCUUUGAAAGAGCUGUG	599	10767	UGCUUUGAAAGAGCUGUG	599	10785	CAGCAGCUGUUCACAAAGCA	2250
10785	GCAGAAUGUAUAGAAUGGU	600	10785	GCAGAAUGUAUAGAAUGGU	600	10803	ACCAUUAUACCAUUCUGC	2251
10803	UCGUACUAUCCUUGGUAGC	601	10803	UCGUACUAUCCUUGGUAGC	601	10821	GCUACCAAGGAUAGUACGA	2252
10821	CACUAUUAUAGAAUAGAG	602	10821	CACUAUUAUAGAAUAGAG	602	10839	CUCAUUCUUAUAAUAGUG	2253
10839	GUUUAACCAUUAUUGAUUU	603	10839	GUUUAACCAUUAUUGAUUU	603	10857	AACAACAAUUGGUGUAAAC	2254
10857	UGUUAAGCAUUGCUGUGU	604	10857	UGUUAAGCAUUGCUGUGU	604	10875	ACCAGCAUUGCUCUAACA	2255
10875	UGUUAACCUUCCAGGUUAG	605	10875	UGUUAACCUUCCAGGUUAG	605	10893	CUUACCUUGGAAGUUAACA	2256
10893	GUUUAAGAAUUAUUGUUAAG	606	10893	GUUUAAGAAUUAUUGUUAAG	606	10911	CUUUAACAAUUAUUAAGAAC	2257
10911	GGGACUUAUUAUUGGAUG	607	10911	GGGACUUAUUAUUGGAUG	607	10929	CAUCCAAUGAUGAGUGCCC	2258
10929	GUUUAACCUUUCUUGACA	608	10929	GUUUAACCUUUCUUGACA	608	10947	UGUCAAGAAAGUUAUAAAGC	2259
10947	AUCACUAUUAUUAUUGUUAU	609	10947	AUCACUAUUAUUAUUGUUAU	609	10965	AACAAGAAUUAUUAAGUUAU	2260
10965	UCAAGUAACACAGUGGUCA	610	10965	UCAAGUAACACAGUGGUCA	610	10983	UGACCAUGUGUUAUUAUUA	2261
10983	ACUGUUUUAUUAUUAUUAU	611	10983	ACUGUUUUAUUAUUAUUAU	611	11001	GUAAACAAAGAAUUAUUAU	2262
11001	CGAGAAUGCUUUCUUGCCA	612	11001	CGAGAAUGCUUUCUUGCCA	612	11019	UGGCAAGAAAGCAUUAUUAU	2263
11019	AUUUAACUUGGUAUUAUUAU	613	11019	AUUUAACUUGGUAUUAUUAU	613	11037	CAUUAUACCAAGAUUAUUAU	2264
11037	GGCAUUAUUGCUUUAUUGCU	614	11037	GGCAUUAUUGCUUUAUUGCU	614	11055	AGCACAUUGCAUUAUUAUUA	2265
11055	UAUGCUUUAUUAUUAUUAU	615	11055	UAUGCUUUAUUAUUAUUAU	615	11073	AUGCUUAACAAAGCAUUAU	2266
11073	UAAGCACGCAUUAUUAUUAU	616	11073	UAAGCACGCAUUAUUAUUAU	616	11091	GCACAAGAAUGCGUUAUUA	2267
11091	CUUGUUUUAUUAUUAUUAU	617	11091	CUUGUUUUAUUAUUAUUAU	617	11109	AGAAGGUUAACAGAAUUAU	2268
11109	UCUUGCAACAGUUAUUAUUAU	618	11109	UCUUGCAACAGUUAUUAUUAU	618	11127	GUAAGCAUUAUUAUUAUUAU	2269
11127	CUUUAUUAUUAUUAUUAUUAU	619	11127	CUUUAUUAUUAUUAUUAUUAU	619	11145	CAUGUAGACCAUUAUUAUUA	2270
11145	GCCUGUUAUUAUUAUUAUUAU	620	11145	GCCUGUUAUUAUUAUUAUUAU	620	11163	CAUACCCAGCAGCAGGCG	2271
11163	GCGUAUUAUUAUUAUUAUUAU	621	11163	GCGUAUUAUUAUUAUUAUUAU	621	11181	AAGCCAUUAUUAUUAUUAU	2272
11181	UGAAUUGGCUUUAUUAUUAU	622	11181	UGAAUUGGCUUUAUUAUUAU	622	11199	GCUAGUGUUAUUAUUAUUA	2273
11199	CUUGUUGGUAUUAUUAUUAU	623	11199	CUUGUUGGUAUUAUUAUUAU	623	11217	AAGCCUAUUAUUAUUAUUAU	2274
11217	UAAGGAUUGUUAUUAUUAU	624	11217	UAAGGAUUGUUAUUAUUAU	624	11235	AUACAUAACCAUUAUUAUUA	2275

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11235	UGCUUACGCUUUAGUUUUG	625	11235	UGCUUACGCUUUAGUUUUG	625	11253	CAAAACUAAAGCUGAAGCA	2276
11253	GCUUUUUCUACGACGCU	626	11253	GCUUUUUCUACGACGCU	626	11271	AGCUGUACUGAAGUAAGC	2277
11271	UGCGACUGUUUAUGAUGAU	627	11271	UGCGACUGUUUAUGAUGAU	627	11289	AUCAUCAAAACAGUGCGA	2278
11289	UGCUGCUAGACGUGUUUGG	628	11289	UGCUGCUAGACGUGUUUGG	628	11307	CCAAACACGUGUAGCAGCA	2279
11307	GACACUGAUGAAUGUCAUU	629	11307	GACACUGAUGAAUGUCAUU	629	11325	AAUGACAUUACAGUGUC	2280
11325	UACACUUGUUUACAAAGUC	630	11325	UACACUUGUUUACAAAGUC	630	11343	GACUUUGUAAACAAAGUGUA	2281
11343	CUACUAUGGUAUUCUUUA	631	11343	CUACUAUGGUAUUCUUUA	631	11361	UAAAGCAUUAACCAUAGUAG	2282
11361	AGAUCAGCUAUUUCCAUG	632	11361	AGAUCAGCUAUUUCCAUG	632	11379	CAUGGAAUUAAGCUUGAUCU	2283
11379	GUGGCCUUAAGUUAUUUCU	633	11379	GUGGCCUUAAGUUAUUUCU	633	11397	AGAAUUAACUAAAGGCCAC	2284
11397	UGUAAACUCUAACUAUUUCU	634	11397	UGUAAACUCUAACUAUUUCU	634	11415	AGAAUUAACUAAAGGCCAC	2285
11415	UGGUGUCGUUACGACUAUC	635	11415	UGGUGUCGUUACGACUAUC	635	11433	GAUAGUCGUAAACGACACCA	2286
11433	CAUGUUUUUAGCUAGAGCU	636	11433	CAUGUUUUUAGCUAGAGCU	636	11451	AGCUCUAGCUAAAAACAUG	2287
11451	UAUAGUGUUUGUGUGUUU	637	11451	UAUAGUGUUUGUGUGUUU	637	11469	AACACACAAAAACACUAUA	2288
11469	UGAGUAUUACCCAUUGUUA	638	11469	UGAGUAUUACCCAUUGUUA	638	11487	UAACAAUGGUAUUAUCUCA	2289
11487	AUUUAUUACUGGCAACACC	639	11487	AUUUAUUACUGGCAACACC	639	11505	GGUGUUGCCAGUAUAAAU	2290
11505	CUUACAGUGUAUCAUGCUU	640	11505	CUUACAGUGUAUCAUGCUU	640	11523	AAGCAUGUAACACUGUAAG	2291
11523	UGUUUAUUUGUUUAGGC	641	11523	UGUUUAUUUGUUUAGGC	641	11541	GCCUAAAGAAACAAUAAACA	2292
11541	CUUUUGUGUGUGCUUAC	642	11541	CUUUUGUGUGUGCUUAC	642	11559	GUAGCAGCAGCAACAAUG	2293
11559	CUUUUGCCUUUCUGUUUA	643	11559	CUUUUGCCUUUCUGUUUA	643	11577	UAAACGAAAGGCCAAAG	2294
11577	ACUAAACCGUUAUUCAGG	644	11577	ACUAAACCGUUAUUCAGG	644	11595	CCUGAAGUAACGGUUGAGU	2295
11595	GCUUACUUGUGUGUUUAU	645	11595	GCUUACUUGUGUGUUUAU	645	11613	AUAAACACCAAGAGUAAGC	2296
11613	UGACUACUUGGUCUCUACA	646	11613	UGACUACUUGGUCUCUACA	646	11631	UGUAGAGACCAAGUAGUCA	2297
11631	ACAAGAAUUUAGGUUAUG	647	11631	ACAAGAAUUUAGGUUAUG	647	11649	CAUAUACCUAAAUUCUUGU	2298
11649	GAACUCCAGGGGUUUUG	648	11649	GAACUCCAGGGGUUUUG	648	11667	CAAAAGCCCGGGGAGUUC	2299
11667	GCCUCCUAAGAGUAUAU	649	11667	GCCUCCUAAGAGUAUAU	649	11685	AUAUACUUCUUAAGGAGGC	2300
11685	UGAUGCUUUCAAGCUUAAAC	650	11685	UGAUGCUUUCAAGCUUAAAC	650	11703	GUUAAGCUUGAAAGCAUCA	2301
11703	CAUUAAGUUUUGGGUAUU	651	11703	CAUUAAGUUUUGGGUAUU	651	11721	AUAACCCCAACACUUAUUG	2302
11721	UGGAGGUAAACCAUGUAUC	652	11721	UGGAGGUAAACCAUGUAUC	652	11739	GAUACAUGGUUUUACCUCCA	2303
11739	CAAGGUUGCUACUGUAACAG	653	11739	CAAGGUUGCUACUGUAACAG	653	11757	CUGUACAGUAGCAACCUUG	2304
11757	GUCUAAAUGUCUGACGUA	654	11757	GUCUAAAUGUCUGACGUA	654	11775	UACGUCAGACAUUUUAGAC	2305
11775	AAAGUGCACAUUCUGUGUA	655	11775	AAAGUGCACAUUCUGUGUA	655	11793	UACCACAGAUUGGACUUAU	2306
11793	ACUGCUCUGGGUUCUCAA	656	11793	ACUGCUCUGGGUUCUCAA	656	11811	UUGAAGAACCAGAGAGAGU	2307
11811	ACAACUUAAGAGUAGAGUCA	657	11811	ACAACUUAAGAGUAGAGUCA	657	11829	UGACUCUACUCUUAAGUUGU	2308
11829	AUCUUCUAAAUUGUGGGCA	658	11829	AUCUUCUAAAUUGUGGGCA	658	11847	UGCCCAAAUUUUAAGAGAU	2309
11847	ACAAGUUAACAACUCCAC	659	11847	ACAAGUUAACAACUCCAC	659	11865	GUGGAGAUUGUACACAUUGU	2310
11865	CAUUGUAUUUCUUCUGCA	660	11865	CAUUGUAUUUCUUCUGCA	660	11883	UGGAAGAAGAAUAUCAUUG	2311
11883	AAAAGACACAACUGAAGCU	661	11883	AAAAGACACAACUGAAGCU	661	11901	AGCUUCAGUUGUGUCUUUU	2312
11901	UUUCGAGAAUGGUUUUCU	662	11901	UUUCGAGAAUGGUUUUCU	662	11919	AGAAACCAUCUUCUCGAAA	2313
11919	UCUUUUGUCUGUUUUGCUA	663	11919	UCUUUUGUCUGUUUUGCUA	663	11937	UAGCAAAACAGACAAAAGA	2314
11937	AUCCAUGCAGGGUGCUGUA	664	11937	AUCCAUGCAGGGUGCUGUA	664	11955	UACAGCACCCUGCAUGGAU	2315
11955	AGACAUUAUAGGUUGUGC	665	11955	AGACAUUAUAGGUUGUGC	665	11973	GCACAACCUUAUUAUGUCU	2316
11973	CGAGGAAAUAGCUCGAUAAC	666	11973	CGAGGAAAUAGCUCGAUAAC	666	11991	GUUAUCGAGCAUUUCCUUG	2317

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11991	CCGUGCUACUCUACAGGCU	667	11991	CCGUGCUACUCUACAGGCU	667	12009	AGCCUGAAGAGUAGCAGG	2318
12009	UAUUGCUUCAGAAUUAUAGU	668	12009	UAUUGCUUCAGAAUUAUAGU	668	12027	ACUAAAUUCUGAAGCAUAU	2319
12027	UUCUUUACCAUAUAUGCC	669	12027	UUCUUUACCAUAUAUGCC	669	12045	GGCAUAUGUUAAGAA	2320
12045	CGCUUAUGCCACUGCCAG	670	12045	CGCUUAUGCCACUGCCAG	670	12063	CUGGGCAGUGGCAUAGCG	2321
12063	GGAGGCCUAUAGCAGGCU	671	12063	GGAGGCCUAUAGCAGGCU	671	12081	AGCCUGCUCAUAGGCCUCC	2322
12081	UGUAGCUAAUGGUAUUCU	672	12081	UGUAGCUAAUGGUAUUCU	672	12099	AGAAUACCAUUAAGCUACA	2323
12099	UGAAGUCGUUCUCAAAG	673	12099	UGAAGUCGUUCUCAAAG	673	12117	CUUUUGAGAAGCAGCUCA	2324
12117	GUUAAAGAAUUCUUAUUAU	674	12117	GUUAAAGAAUUCUUAUUAU	674	12135	AUCAAAGAUUUUCUUUAA	2325
12135	UGUGGCCUAAUUCUGAGUUAU	675	12135	UGUGGCCUAAUUCUGAGUUAU	675	12153	AAUCAGAUUUUAGCCACA	2326
12153	UGACCGUGAUGUGGCAUAG	676	12153	UGACCGUGAUGUGGCAUAG	676	12171	CAUGGCAGCAUCACGGUCA	2327
12171	GCAACGCAAGUUGGAAAG	677	12171	GCAACGCAAGUUGGAAAG	677	12189	CUUUUCCAAUUCGCUUGC	2328
12189	GAUGGCAGAUACAGGCUAUG	678	12189	GAUGGCAGAUACAGGCUAUG	678	12207	CAUAGCCUGAUCUGCCAUUC	2329
12207	GACCCAAUUGUACAAACAG	679	12207	GACCCAAUUGUACAAACAG	679	12225	CUGUUUGUACAUUUUGGGUC	2330
12225	GGCAAGAUUCUGAGCAAG	680	12225	GGCAAGAUUCUGAGCAAG	680	12243	CUUGUCCUCAGAUUUUGCC	2331
12243	GAGGGCAAAAGUAACUAGU	681	12243	GAGGGCAAAAGUAACUAGU	681	12261	ACUAGUACUUUUUGCCUC	2332
12261	UGCUAUGCAAAACAUUGCUC	682	12261	UGCUAUGCAAAACAUUGCUC	682	12279	GAGCAUUUUUGCAUAGCA	2333
12279	CUUCAGAUUCUAGGAAG	683	12279	CUUCAGAUUCUAGGAAG	683	12297	CUUCCUAAGCAUAGUGAAG	2334
12297	GCUGUAUAUAGUACACU	684	12297	GCUGUAUAUAGUACACU	684	12315	AAGUGCAUUAUUAACAAGC	2335
12315	UAACAACAUUAUACAACU	685	12315	UAACAACAUUAUACAACU	685	12333	AUUGUUAUUAUUGUUA	2336
12333	UGCGGUGAUGGUUGUUGU	686	12333	UGCGGUGAUGGUUGUUGU	686	12351	AACAACAACUACCGCGCA	2337
12351	UCCACUACAACUACCA	687	12351	UCCACUACAACUACCA	687	12369	UGGUAUGUUGUAGUGGA	2338
12369	AUUGACUACAGCAGCCAA	688	12369	AUUGACUACAGCAGCCAA	688	12387	UUUGGUGUGUGUAGUCAA	2339
12387	ACUCAUGGUUGUUGUCCU	689	12387	ACUCAUGGUUGUUGUCCU	689	12405	AGGACAACAACCAUGAGU	2340
12405	UGAUUAUGGUACCUAAC	690	12405	UGAUUAUGGUACCUAAC	690	12423	CUUGUAGGUACCAUUAU	2341
12423	GAACCUUUAUAGUAGU	691	12423	GAACCUUUAUAGUAGU	691	12441	GUUACCAUACAAGUGUUC	2342
12441	CACCUUUAUAGUAGU	692	12441	CACCUUUAUAGUAGU	692	12459	AGAUCAUUAUUAAGGUG	2343
12459	UGCACUCUGGAAUCCAG	693	12459	UGCACUCUGGAAUCCAG	693	12477	CUGGAUUUCCAGAGUGCA	2344
12477	GCAAGUUGUAGUGCGAU	694	12477	GCAAGUUGUAGUGCGAU	694	12495	AUCGCAUCAACAACUUGC	2345
12495	UAGCAAGAUUGUUAACU	695	12495	UAGCAAGAUUGUUAACU	695	12513	AAGUUGAACAUCUUGCUA	2346
12513	UAGUAAAUUAACUAGGAC	696	12513	UAGUAAAUUAACUAGGAC	696	12531	GUCCAUGUUAUUUCACUA	2347
12531	CAAUUACCAAAUUAUUGCU	697	12531	CAAUUACCAAAUUAUUGCU	697	12549	AGCAAAUUAUUGGUAUUG	2348
12549	UUGGCCUUAUUAUUAUUA	698	12549	UUGGCCUUAUUAUUAUUA	698	12567	UGUAAACAUAAGAGGCCAA	2349
12567	AGCUCUAAGAGCCAAUUA	699	12567	AGCUCUAAGAGCCAAUUA	699	12585	UGAGUUGGCUUAUAGAGCU	2350
12585	AGCUGUUAACUACAGAAU	700	12585	AGCUGUUAACUACAGAAU	700	12603	AUUCUGUUAUUAACAGCU	2351
12603	UAAUAAACUAGUCCAGUA	701	12603	UAAUAAACUAGUCCAGUA	701	12621	UACUGGACUCAGUUAUUA	2352
12621	AGCACUACAGAGUUGCC	702	12621	AGCACUACAGAGUUGCC	702	12639	GGCAUCUCUGCUGUAGUGCU	2353
12639	CUGUGCGGCUUGUACACCA	703	12639	CUGUGCGGCUUGUACACCA	703	12657	UGUGUACCAAGCCGACAG	2354
12657	ACAAACAGCUUUGUACUAGU	704	12657	ACAAACAGCUUUGUACUAGU	704	12675	AUCAGUACAGCUGUUAUUG	2355
12675	UGACAAUGCAGUUGCCUAC	705	12675	UGACAAUGCAGUUGCCUAC	705	12693	GUAGGCAAGUGCAUUGUCA	2356
12693	CUAUAACAUAUUGGAAGGA	706	12693	CUAUAACAUAUUGGAAGGA	706	12711	UCCCUUGAAUUGUUAUAG	2357
12711	AGGUAGGUUUGUGUGGCA	707	12711	AGGUAGGUUUGUGUGGCA	707	12729	UGCCAGCACAAACCUACCU	2358
12729	AUUACUACAGACCAACCA	708	12729	AUUACUACAGACCAACCA	708	12747	UUUGGUGGUCUAGUUAUUA	2359

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12747	AGAUUCUCAAUUGGCUAGA	709	12747	AGAUUCUCAAUUGGCUAGA	709	12765	UCUAGCCCAUUIUGAGAUUC	2360
12765	AUUCUUAAGAGUGAGGU	710	12765	AUUCUUAAGAGUGAGGU	710	12783	ACCAUCACUCUUAAGGAAU	2361
12783	UACAGGUACAUIUUAACACA	711	12783	UACAGGUACAUIUUAACACA	711	12801	UGUGUAAUUGUACCUGUA	2362
12801	AGAAGUGAACCAACCUUGU	712	12801	AGAAGUGAACCAACCUUGU	712	12819	ACAAGGUGUUCAGUUCU	2363
12819	UAGGUUUGUUAACAGACACA	713	12819	UAGGUUUGUUAACAGACACA	713	12837	UGUGUCUGUAACAACACCUA	2364
12837	ACAAAAGGGCUAAAGUG	714	12837	ACAAAAGGGCUAAAGUG	714	12855	CACUUUAGGCCCUUUUGGU	2365
12855	GAAUACUUGUAACUUAUC	715	12855	GAAUACUUGUAACUUAUC	715	12873	UAGGUUUGUUAAGCCUUG	2366
12873	CAAAGGUUAACAACCUA	716	12873	CAAAGGUUAACAACCUA	716	12891	CAGCACCACUACCUUAUU	2367
12891	AAUAGAGGUUUGGUGUG	717	12891	AAUAGAGGUUUGGUGUG	717	12909	UGUAGCAGCUAAACUGCCC	2368
12909	GGCAGUUUAGCUGCUACA	718	12909	GGCAGUUUAGCUGCUACA	718	12927	UCCAGCCUGAAGAGCUACU	2369
12927	AGUACGUCUUCAGGCUUGA	719	12927	AGUACGUCUUCAGGCUUGA	719	12945	AGGUACUUCUGUAGCAUUC	2370
12945	AAUUGCUACAGAAUACCU	720	12945	AAUUGCUACAGAAUACCU	720	12963	AAGCACAGUUGAAUUGGCA	2371
12963	UGCCAAUUAACUGUGCUU	721	12963	UGCCAAUUAACUGUGCUU	721	12981	UGCAAAAGCACAGAAAGGAA	2372
12981	UUCUUCUGUGCUUUUGCA	722	12981	UUCUUCUGUGCUUUUGCA	722	12999	UGCUUAGCAGGGUCUACU	2373
12999	AGUAGACCCUGCUAAAGCA	723	12999	AGUAGACCCUGCUAAAGCA	723	13017	UGCUUAGCAGGGUCUACU	2374
13017	AUAAGAGGUUAUUAACGCA	724	13017	AUAAGAGGUUAUUAACGCA	724	13035	GUUAGGUUAUUAUUAUUA	2375
13035	AAGUGGAGGACAACCAUUC	725	13035	AAGUGGAGGACAACCAUUC	725	13053	GAUUGGUUGUCCUCCACU	2376
13053	CACCAACUGUGUAGGAUG	726	13053	CACCAACUGUGUAGGAUG	726	13071	CAUUCUACACAGUUGGUG	2377
13071	GUUGUGUACACACACUGGU	727	13071	GUUGUGUACACACACUGGU	727	13089	ACCAGUGUGUACACAAAC	2378
13089	UACAGGACAGGCAUUAUCU	728	13089	UACAGGACAGGCAUUAUCU	728	13107	AGUAAUUGCCUGUCCUGUA	2379
13107	UGUAAACACAGAGCUAAC	729	13107	UGUAAACACAGAGCUAAC	729	13125	GUUAGCUUCUGGUGUUAACA	2380
13125	CAUGGACCAAGAGUCCUUU	730	13125	CAUGGACCAAGAGUCCUUU	730	13143	AAAGGACUCUUGGUCUUG	2381
13143	UGGUGUGUUAUUAUUGU	731	13143	UGGUGUGUUAUUAUUGU	731	13161	ACAACAUGAAGACACACCA	2382
13161	UCUGUUAUUGUAUAGCCAC	732	13161	UCUGUUAUUGUAUAGCCAC	732	13179	GUGGCAUUAACAUAACAGA	2383
13179	CAUUGACCAUCCAAUCCU	733	13179	CAUUGACCAUCCAAUCCU	733	13197	AGGAUUGGAGUUGUUAUG	2384
13197	UAAAGGAUUCUGUACUUG	734	13197	UAAAGGAUUCUGUACUUG	734	13215	CAAGUCACAGAAUCCUUA	2385
13215	GAAAGGUAAUAGCUCCAA	735	13215	GAAAGGUAAUAGCUCCAA	735	13233	UUGGACGUACUUAACCUUC	2386
13233	AAUACCUACCAUUGUGCU	736	13233	AAUACCUACCAUUGUGCU	736	13251	AGCACAAGUGGUAAGUUAU	2387
13251	UAAUGACCCAGUGGGUUUU	737	13251	UAAUGACCCAGUGGGUUUU	737	13269	AAACCCACUGGGUUAUA	2388
13269	UACACUUAAGAAACACAGUC	738	13269	UACACUUAAGAAACACAGUC	738	13287	GACUGUUAUUAAGUGUA	2389
13287	CUGUACCGUCUGCGGAAUG	739	13287	CUGUACCGUCUGCGGAAUG	739	13305	CAUUCGACAGCGGUACAG	2390
13305	GUGGAAAGGUUAUGGCUUG	740	13305	GUGGAAAGGUUAUGGCUUG	740	13323	ACAGCCAUAAACCUUUCAC	2391
13323	UAGUUGUAGCAACUCCGC	741	13323	UAGUUGUAGCAACUCCGC	741	13341	CGGAGUUGGUCACACUA	2392
13341	CGAACCCUUGAUGCAGUCU	742	13341	CGAACCCUUGAUGCAGUCU	742	13359	AGACUGCAUUAAGGUUCG	2393
13359	UGCGGAUGCAUUAACGUUU	743	13359	UGCGGAUGCAUUAACGUUU	743	13377	AAACGUUGAUGCAUCCGCA	2394
13377	UUUAAACGGUUUGCGGUG	744	13377	UUUAAACGGUUUGCGGUG	744	13395	CACCGCAAAACCCGUUUA	2395
13395	GUAAGUGCAGCCCGUCUUA	745	13395	GUAAGUGCAGCCCGUCUUA	745	13413	UAGACGGGCGUCACUAC	2396
13413	ACACCGUGCGGCACAGGCA	746	13413	ACACCGUGCGGCACAGGCA	746	13431	UGCCUGUGCGGCACGGUGU	2397
13431	ACUAGUACUGAUGUCGUCU	747	13431	ACUAGUACUGAUGUCGUCU	747	13449	AGACGACAUACAGUACUAGU	2398
13449	UACAGGGCUUUUGAUUUU	748	13449	UACAGGGCUUUUGAUUUU	748	13467	AAAUACAAAAGCCCUUA	2399
13467	UACAACGAAAAAGUUGCUG	749	13467	UACAACGAAAAAGUUGCUG	749	13485	CAGCAACUUAUUCGUUGUA	2400
13485	GGUUUUGCAAAGUUCUUA	750	13485	GGUUUUGCAAAGUUCUUA	750	13503	UUAGGAACUUAUGCAAAACC	2401

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13503	AAAACUAAUUGCUGCGCU	751	13503	AAAACUAAUUGCUGCGCU	751	13521	AGCGACGCAAUUAGUUUU	2402
13521	UUCGAGGAGAGGAGG	752	13521	UUCGAGGAGAGGAGG	752	13539	CCUCAUCCUUCUGGAA	2403
13539	GAAGGCAUUUUAUAGACU	753	13539	GAAGGCAUUUUAUAGACU	753	13557	AGUCUAAUAAUUGCCUUC	2404
13557	UCUACUUUUGUAGUUAAGA	754	13557	UCUACUUUUGUAGUUAAGA	754	13575	UCUUAACUACAAAGUAAGA	2405
13575	AGGCAUACUAGUCUACU	755	13575	AGGCAUACUAGUCUACU	755	13593	AGUUAGACAUAGUAGCCU	2406
13593	UACCAACAUAGAGAGACU	756	13593	UACCAACAUAGAGAGACU	756	13611	UAGUCUUCUAGUUGGUA	2407
13611	AUUUAACUUGGUUAAG	757	13611	AUUUAACUUGGUUAAG	757	13629	CUUUAACCAAGUUUAAU	2408
13629	GAUUGCCAGCGUUGCUG	758	13629	GAUUGCCAGCGUUGCUG	758	13647	CAGCAACCGUGGACAAUC	2409
13647	GUCCAUGACUUUUCAAGU	759	13647	GUCCAUGACUUUUCAAGU	759	13665	ACUUGAAAAGUCAUGGAC	2410
13665	UUUAGAGUAGUGGACAC	760	13665	UUUAGAGUAGUGGACAC	760	13683	UGUACCAUCUACUCUAAA	2411
13683	AUGGUACCAUAUAUCAC	761	13683	AUGGUACCAUAUAUCAC	761	13701	GUGAUUAUUGGUAGCCAU	2412
13701	CGUCAGCGUCUAACUAAU	762	13701	CGUCAGCGUCUAACUAAU	762	13719	AUUUAGUUAGACGCGACG	2413
13719	UACACAAUGGCUGAUUUAG	763	13719	UACACAAUGGCUGAUUUAG	763	13737	CUAAUUCAGCCAUUGUGUA	2414
13737	GUCUAGUCUCUACGUCU	764	13737	GUCUAGUCUCUACGUCU	764	13755	AUUGACGUAGAGCAUAGAC	2415
13755	UUUGAUGAGGGUAAUUG	765	13755	UUUGAUGAGGGUAAUUG	765	13773	CACAAUUGCCUACUACAA	2416
13773	GAUACAUUAAAAGAAUAC	766	13773	GAUACAUUAAAAGAAUAC	766	13791	GUUUUUCUUUAAUUGUAC	2417
13791	CUCGUCACAUACAAUUGCU	767	13791	CUCGUCACAUACAAUUGCU	767	13809	AGCAUUUGUAGUGACGAG	2418
13809	UGUGAUGAUAUUUAUUA	768	13809	UGUGAUGAUAUUUAUUA	768	13827	UGAAUUAUUAUUAUUA	2419
13827	AAUAAAGAGGUUGGUAG	769	13827	AAUAAAGAGGUUGGUAG	769	13845	CAUACCAUCCUUCUUAU	2420
13845	GACUUCGUAGAGAAUCCUG	770	13845	GACUUCGUAGAGAAUCCUG	770	13863	CAGGAUUCUUCUACGAAGUC	2421
13863	GACUUCUACGCGUAUAUG	771	13863	GACUUCUACGCGUAUAUG	771	13881	CAUAUACGCGUAAAGUAGUC	2422
13881	GUACUUCUAGGUGAGCGUG	772	13881	GUACUUCUAGGUGAGCGUG	772	13899	CACGUCACUUAAGUUUAGC	2423
13899	GUACGCCAAUUAUUA	773	13899	GUACGCCAAUUAUUA	773	13917	UUAAUUAUUAUUAUUA	2424
13917	AAGACUGUACAAUUCUGCG	774	13917	AAGACUGUACAAUUCUGCG	774	13935	CGCAGAAUUGUAGGAGUCU	2425
13935	GAUGCUAUGCGUGAUGCAG	775	13935	GAUGCUAUGCGUGAUGCAG	775	13953	CUGCAUCACGCAUAGCAUC	2426
13953	GGCAUUGUAGCGUACUGA	776	13953	GGCAUUGUAGCGUACUGA	776	13971	UCAGUACGCCUACAAUCC	2427
13971	ACAUUAGAUUAUAGGAUC	777	13971	ACAUUAGAUUAUAGGAUC	777	13989	GAUCCUGAUUAUUAUUA	2428
13989	CUUAAUGGGAAUUGGUACG	778	13989	CUUAAUGGGAAUUGGUACG	778	14007	CGUACCAUUGUCCAUUAAG	2429
14007	GAUUUGGGUAGUUUCGUAC	779	14007	GAUUUGGGUAGUUUCGUAC	779	14025	GUACGAAUUCACCGAAUUC	2430
14025	CAAGUAGCACCGGUGCG	780	14025	CAAGUAGCACCGGUGCG	780	14043	CGCAGCCUGGUGCUACUUG	2431
14043	GGAGUUCUUAUUGGUAU	781	14043	GGAGUUCUUAUUGGUAU	781	14061	AUCCACAAUAGGAACUCC	2432
14061	UCAUUAUUAUUAUUA	782	14061	UCAUUAUUAUUAUUA	782	14079	UCAGCAUUAUUAUUAUUA	2433
14079	AUGCCCAUCCUACUUAUGA	783	14079	AUGCCCAUCCUACUUAUGA	783	14097	UCAAAUGAGGAGUAGGCAU	2434
14097	ACUAGGGCAUUGGCGUCUG	784	14097	ACUAGGGCAUUGGCGUCUG	784	14115	CAGCAGCAUUGCCCUAGU	2435
14115	GAGUCCCAUUAUGGAGUCUG	785	14115	GAGUCCCAUUAUGGAGUCUG	785	14133	CAGCAUCCAUUAUGGAGUC	2436
14133	GAUCUGGCAAAACCAUUA	786	14133	GAUCUGGCAAAACCAUUA	786	14151	UAAGUGGUUUUGCGAGAU	2437
14151	AUUAAUGGGUUAUUGCUGA	787	14151	AUUAAUGGGUUAUUGCUGA	787	14169	UCAGCAAAUCCCAUUAU	2438
14169	AAUUAUGAUUUUACGGAAG	788	14169	AAUUAUGAUUUUACGGAAG	788	14187	CUUCCGUAUUAUUAUUA	2439
14187	GAGACAUUUUGUCUUCUG	789	14187	GAGACAUUUUGUCUUCUG	789	14205	CGAAGACAAUUAUUAUUA	2440
14205	GACCGUUAUUUAUUAUUA	790	14205	GACCGUUAUUUAUUAUUA	790	14223	AAUUAUUAUUAUUAUUA	2441
14223	UGGGACCAUUAUUAUUAUUA	791	14223	UGGGACCAUUAUUAUUAUUA	791	14241	GAUGGUUAUUGGUGGCGCA	2442
14241	CCCAUUUGAUUAUUAUUAUUA	792	14241	CCCAUUUGAUUAUUAUUAUUA	792	14259	AACAGUUAUUAUUAUUAUUA	2443

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14259	UUGGAUGAUGGUGUAUCC	793	14259	UUGGAUGAUGGUGUAUCC	793	14277	GGAAACACCUAUAUCCAA	2444
14277	CUUCAUUGGCAAAUUA	794	14277	CUUCAUUGGCAAAUUA	794	14295	UAAAGUUUGCACAUAAG	2445
14295	AAUGUUUAUUUUAUACUG	795	14295	AAUGUUUAUUUUAUACUG	795	14313	CAGUAGAAAUAAACACAUU	2446
14313	GUGUUUCCACCUACAAGUU	796	14313	GUGUUUCCACCUACAAGUU	796	14331	AACUUUGAGGUGAAACAC	2447
14331	UUUGGACCAUAUAAGAA	797	14331	UUUGGACCAUAUAAGAA	797	14349	UUUUUUAUAGUGGUCCAAA	2448
14349	AAAUUUUUUAAGUGGUG	798	14349	AAAUUUUUUAAGUGGUG	798	14367	CACCAUCUACAAAUUUUU	2449
14367	GUUCCUUUUUGUUUCAA	799	14367	GUUCCUUUUUGUUUCAA	799	14385	UUGAAACCAACAAAGGAAC	2450
14385	ACUGGAUCCAUUUUUGUG	800	14385	ACUGGAUCCAUUUUUGUG	800	14403	CACGAAAUUGUAUCCAGU	2451
14403	GAGUAGGAGUGUAACUA	801	14403	GAGUAGGAGUGUAACUA	801	14421	UAUAGCAGCUCCUAACUC	2452
14421	AAUCAGGAUGUAACUUA	802	14421	AAUCAGGAUGUAACUUA	802	14439	GUAAGUUUACAUCCUGAUU	2453
14439	CAUAGCUGGUGUCAGUU	803	14439	CAUAGCUGGUGUCAGUU	803	14457	AACUGAGACGCGAGCUAUG	2454
14457	UUAAGGAACUUUUAUGUG	804	14457	UUAAGGAACUUUUAUGUG	804	14475	ACACUAAAGUUCCUUGAA	2455
14475	UAUGCUGCUGAUCCAGCUA	805	14475	UAUGCUGCUGAUCCAGCUA	805	14493	UAGCUGGACGACGACUA	2456
14493	AUGCAUGCAGCUUCUGGCA	806	14493	AUGCAUGCAGCUUCUGGCA	806	14511	UGCCAGAAGCUGCAUGCAU	2457
14511	AAUUUAUUGUAUAAC	807	14511	AAUUUAUUGUAUAAC	807	14529	GUUUUAUCUAGCAUAAUUU	2458
14529	CGCACUACAUUUUUAUG	808	14529	CGCACUACAUUUUUAUG	808	14547	CUGAAAGCAUGUAGUGCG	2459
14547	GUAGCUGCACUAACAAACA	809	14547	GUAGCUGCACUAACAAACA	809	14565	UGUUUGUAGUGCAGCUAC	2460
14565	AAUGUUGCUUUUCAAACUG	810	14565	AAUGUUGCUUUUCAAACUG	810	14583	CAGUUUGAAAGCAACAUU	2461
14583	GUCAAACCGGUAUUUUUA	811	14583	GUCAAACCGGUAUUUUUA	811	14601	UAAAUUUAACCGGUUUGAC	2462
14601	AAUAAAGACUUUUAUGACU	812	14601	AAUAAAGACUUUUAUGACU	812	14619	AGUCAUAAAGUUUUUAUU	2463
14619	UUUGCUGUGUUAAGGUU	813	14619	UUUGCUGUGUUAAGGUU	813	14637	AACCUUUAAGACACAGCAA	2464
14637	UUCUUUAAGGAAGGAAGUU	814	14637	UUCUUUAAGGAAGGAAGUU	814	14655	AACUUCUUCUUAAGAA	2465
14655	UCUUUUGAUAACAAACACU	815	14655	UCUUUUGAUAACAAACACU	815	14673	AGUGUUUUAUUAUCAAACA	2466
14673	UUUUUUGUUGCUAGGAUG	816	14673	UUUUUUGUUGCUAGGAUG	816	14691	CAUCCUGAGCAAAAGAA	2467
14691	GGCAACGUGCUAGGAGUG	817	14691	GGCAACGUGCUAGGAGUG	817	14709	CACUGAGACGCGUUGCC	2468
14709	GAUUUAUGACUAUUUAUCGUU	818	14709	GAUUUAUGACUAUUUAUCGUU	818	14727	AACGAUAAUAGUCAUAUC	2469
14727	UAUAAUCUGCCAAACAUGU	819	14727	UAUAAUCUGCCAAACAUGU	819	14745	ACAUUGUUGGCAUAUAUA	2470
14745	UGUGAUAUCAGACAACUCC	820	14745	UGUGAUAUCAGACAACUCC	820	14763	GGAGUUGUCUGAUUAUCA	2471
14763	CUAUUCGUAUUUAAGUUG	821	14763	CUAUUCGUAUUUAAGUUG	821	14781	CAACUUCACUACGAAUAG	2472
14781	GUUGAUAUAUUAUUAUUAU	822	14781	GUUGAUAUAUUAUUAUUAU	822	14799	AUCAAAGUAUUUAUCAAC	2473
14799	UGUUACGAUGGUGGUGUA	823	14799	UGUUACGAUGGUGGUGUA	823	14817	UACAGCCACCAUGUAACA	2474
14817	AUUAAUGCCAAACCAAGUAA	824	14817	AUUAAUGCCAAACCAAGUAA	824	14835	UUACUUGGUUGGCAUUAU	2475
14835	AUCGUUAACAUCUGGAUA	825	14835	AUCGUUAACAUCUGGAUA	825	14853	UAUCCAGUAUUAUUAACGUA	2476
14853	AAUACAGCUGGUUUCUCCAU	826	14853	AAUACAGCUGGUUUCUCCAU	826	14871	AUGGAAACCAAGCUGAUUU	2477
14871	UUUAAUAAUUGGGUUAAGG	827	14871	UUUAAUAAUUGGGUUAAGG	827	14889	CCUAAACCCAUUUUAUAAA	2478
14889	GCUAGACUUUAUUAUGACU	828	14889	GCUAGACUUUAUUAUGACU	828	14907	AGUCAUAAUAAAGUCUAGC	2479
14907	UCAUAGUAUUAUGGGAUC	829	14907	UCAUAGUAUUAUGGGAUC	829	14925	GAUCCUCAUAACUUAUGA	2480
14925	CAAGAUGCACUUUUCGCGU	830	14925	CAAGAUGCACUUUUCGCGU	830	14943	ACGCGAAAGUGCAUCUUG	2481
14943	UAUACUAAGCGUAUUGUCA	831	14943	UAUACUAAGCGUAUUGUCA	831	14961	UGACAUUAACGCUUAGUAUA	2482
14961	AUGCCUACUAUAACUCAAA	832	14961	AUGCCUACUAUAACUCAAA	832	14979	UUUGAGUUAUAGAGGGAU	2483
14979	AUGAAUCUUAAGUAUGCCA	833	14979	AUGAAUCUUAAGUAUGCCA	833	14997	UGGCAUACUUAAGAUUCAU	2484
14997	AUUAGUGCAAAAGAAUAGAG	834	14997	AUUAGUGCAAAAGAAUAGAG	834	15015	CUCUAUUCUUAUGCACUAU	2485

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15015	GCUCGACCGUAGCUGGUG	835	15015	GCUCGACCGUAGCUGGUG	835	15033	CACGAGCUACGGUGCGAGC	2486
15033	GUCUCUAUCUGUAGUACUA	836	15033	GUCUCUAUCUGUAGUACUA	836	15051	UAGUACUACAGAUAGAGAC	2487
15051	AUGACAAUAGACAGUUUC	837	15051	AUGACAAUAGACAGUUUC	837	15069	GAACUGUCUAUUUGUCAU	2488
15069	CAUCAGAAUUAUUGAAGU	838	15069	CAUCAGAAUUAUUGAAGU	838	15087	ACUUAUUAUUUUCUGAUG	2489
15087	UCAUAGCCGCCACUAGAG	839	15087	UCAUAGCCGCCACUAGAG	839	15105	CUCUAGUGGCGGUUAUGA	2490
15105	GGAGCUACUGUGUAUUUG	840	15105	GGAGCUACUGUGUAUUUG	840	15123	CAAUUACACAGUAGCUCC	2491
15123	GGAAACAAGCAUUAUACG	841	15123	GGAAACAAGCAUUAUACG	841	15141	CGUAAACUUGCUUGUCC	2492
15141	GGUGGUGGCAUUAUUGU	842	15141	GGUGGUGGCAUUAUUGU	842	15159	ACAUUAUUGCCAGCCACC	2493
15159	UUAUAAACUGUUUACAGUG	843	15159	UUAUAAACUGUUUACAGUG	843	15177	CACUGUAAACAGUUUUAA	2494
15177	GAUGUAGAAACUCCACACC	844	15177	GAUGUAGAAACUCCACACC	844	15195	GGUGUGGAGUUUCUACAU	2495
15195	CUUAUGGUGGGAUUAUC	845	15195	CUUAUGGUGGGAUUAUC	845	15213	GAUAAUCCCAACCCAUAA	2496
15213	CCAAUUGUGACAGAGCCA	846	15213	CCAAUUGUGACAGAGCCA	846	15231	UGGUCUCUGUACAUUUUGG	2497
15231	AUGCCUAAACAGUUAAGGA	847	15231	AUGCCUAAACAGUUAAGGA	847	15249	UCCUAAAGCAUUAAGGCAU	2498
15249	AUAUAGCCUCUUAUUGU	848	15249	AUAUAGCCUCUUAUUGU	848	15267	GAACAAGAGAGGCCAUUAU	2499
15267	CUUGCUCGCAACAUAACA	849	15267	CUUGCUCGCAACAUAACA	849	15285	UGUUAUGUUUGCGAGCAAG	2500
15285	ACUUGCUGUAACUUAUCAC	850	15285	ACUUGCUGUAACUUAUCAC	850	15303	GUGUAAGUUUACAGCAAGU	2501
15303	CACCGUUAUACAGGUUAG	851	15303	CACCGUUAUACAGGUUAG	851	15321	CUAACCUUGUAGAAACGGUG	2502
15321	GUAAACGAGUGGCGCAAG	852	15321	GUAAACGAGUGGCGCAAG	852	15339	CUUGCGCACACUCGUUAGC	2503
15339	GUUAUAGUGAGAGUGUCA	853	15339	GUUAUAGUGAGAGUGUCA	853	15357	UGACAUUCACUUUAUAC	2504
15357	AUGUGUGGGGUCACUUAU	854	15357	AUGUGUGGGGUCACUUAU	854	15375	AUAGUGACCGCCACACAU	2505
15375	UAUGUUAACACAGGUGAA	855	15375	UAUGUUAACACAGGUGAA	855	15393	UUCACCCUGUUUAACAU	2506
15393	ACAUCUCCGGUGAUGCUA	856	15393	ACAUCUCCGGUGAUGCUA	856	15411	UAGCAUCACCGGAUGAUGU	2507
15411	ACAACUGCUUAUGCUAAUA	857	15411	ACAACUGCUUAUGCUAAUA	857	15429	UAUAGCAUAAAGCAUUGU	2508
15429	AGUGUCUUUAACAUUUUGC	858	15429	AGUGUCUUUAACAUUUUGC	858	15447	GACAAUUGUUAAGACACU	2509
15447	CAAGCUGUUAACAGCCAAUG	859	15447	CAAGCUGUUAACAGCCAAUG	859	15465	CAUUGGUGUUAACAGCUUG	2510
15465	GUAAUAGCACUUAUUAACA	860	15465	GUAAUAGCACUUAUUAACA	860	15483	UUGAAAGAGUGCAUUAUAC	2511
15483	ACUGAUGGUAUAAGAUAG	861	15483	ACUGAUGGUAUAAGAUAG	861	15501	CUAUCUUAUUUACCAUCAGU	2512
15501	GCUGACAAGUAUUGCCGCA	862	15501	GCUGACAAGUAUUGCCGCA	862	15519	UGCGGACAUACUUGUCAGC	2513
15519	AUCUACAACACAGGCUCU	863	15519	AUCUACAACACAGGCUCU	863	15537	AGAGCCUGUUAUUGAUAU	2514
15537	UAUGAGUGUCUUAUAGAA	864	15537	UAUGAGUGUCUUAUAGAA	864	15555	UUCUAUAGAGACACUCAU	2515
15555	AUAAGGGAUGUUAUGAUCU	865	15555	AUAAGGGAUGUUAUGAUCU	865	15573	CAUGAUCAACAUCUCCUAU	2516
15573	GAUUUCGUGGAUGAGUUUU	866	15573	GAUUUCGUGGAUGAGUUUU	866	15591	AAAACUACUCCAGAAUUC	2517
15591	UACGCUUACCGGUAUAAAC	867	15591	UACGCUUACCGGUAUAAAC	867	15609	GUUUAAGGAGGUUAAGCGUA	2518
15609	CAUUCUCCAUGAUAUUC	868	15609	CAUUCUCCAUGAUAUUC	868	15627	GAUCAUCAUGGAGAAUUG	2519
15627	CUUUCUGAUGAUGCCGUUG	869	15627	CUUUCUGAUGAUGCCGUUG	869	15645	CAACGGCAUCAUCAGAAAG	2520
15645	GUGUGCUUAUACAGUAACU	870	15645	GUGUGCUUAUACAGUAACU	870	15663	AGUUAACUGUUUAAGCACAC	2521
15663	UAUGCGGCUCAAGGUUUAG	871	15663	UAUGCGGCUCAAGGUUUAG	871	15681	CUAAACCUUAGCCGCAU	2522
15681	GUAGCAGCAUUAAGAAACU	872	15681	GUAGCAGCAUUAAGAAACU	872	15699	AGUUAUUAUAGCUAGCUAC	2523
15699	UUUAAGGCAUUAUUAU	873	15699	UUUAAGGCAUUAUUAU	873	15717	AUAUAAAGAACUGCCUUA	2524
15717	UAUCAAUUAUUAUGUUA	874	15717	UAUCAAUUAUUAUGUUA	874	15735	UGAACACAUUAUUUUGAUA	2525
15735	AUGUCUGAGGCAAAUUGU	875	15735	AUGUCUGAGGCAAAUUGU	875	15753	AACAUUUUGCCUCAGACAU	2526
15753	UGGACUGAGACUGACCUUA	876	15753	UGGACUGAGACUGACCUUA	876	15771	UAAGGUGACUGUCAGUCCA	2527

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15771	ACUAAAGGACCUCACGAU	877	15771	ACUAAAGGACCUCACGAU	877	15789	AUUCGUGAGGUCCUUUAGU	2528
15789	UUUUGCUCACAGCAUACAA	878	15789	UUUUGCUCACAGCAUACAA	878	15807	UUGUAUGCUGUGAGCAAAA	2529
15807	AUGCUAGUUAAACAAGGAG	879	15807	AUGCUAGUUAAACAAGGAG	879	15825	CUCUUGUUUAAACUAGCAU	2530
15825	GAUGAUUACGUGUACCUUG	880	15825	GAUGAUUACGUGUACCUUG	880	15843	GCAGGUACACGUAUACUAC	2531
15843	CCUUAACCCAGAUCCAUCAA	881	15843	CCUUAACCCAGAUCCAUCAA	881	15861	UUGAUGGAUCUGGGUAAAG	2532
15861	AGAAUUAUAGGCGCAGGCU	882	15861	AGAAUUAUAGGCGCAGGCU	882	15879	AGCCUGCGCCUAAUUAUCU	2533
15879	UGUUUUGCUGAUGAUUAUG	883	15879	UGUUUUGCUGAUGAUUAUG	883	15897	CAAUUAUCGACAAAAACA	2534
15897	GUCAAAACAGUAGGUACAC	884	15897	GUCAAAACAGUAGGUACAC	884	15915	GUAUACCAUCUGUUUUGAC	2535
15915	CUUAUGAUUAGAAAGGUUG	885	15915	CUUAUGAUUAGAAAGGUUG	885	15933	CGAACCUUUAUUAUUAAG	2536
15933	GUGUCACUGGCUUAUUAUG	886	15933	GUGUCACUGGCUUAUUAUG	886	15951	CAUCAUAAGCCAGUGACAC	2537
15951	GCUUACCCACUUAACAAAC	887	15951	GCUUACCCACUUAACAAAC	887	15969	GUUUUGUAAGUGGGUAAAG	2538
15969	CAUCCUUAUCAGGAGUAUG	888	15969	CAUCCUUAUCAGGAGUAUG	888	15987	CAUACUCCUGAUUAGGAUG	2539
15987	GCUGAUGUCUUUACCUUGU	889	15987	GCUGAUGUCUUUACCUUGU	889	16005	ACAAGUGAAAGACAUACGC	2540
16005	UAUUUACAAUACAUUAGAA	890	16005	UAUUUACAAUACAUUAGAA	890	16023	UUCUAUUGUAUUGUAAUA	2541
16023	AAGUUAUUAUGAGGCUUA	891	16023	AAGUUAUUAUGAGGCUUA	891	16041	UAGCUCUAUUGUAACUU	2542
16041	ACUGGCCACAUUUGGACA	892	16041	ACUGGCCACAUUUGGACA	892	16059	UUGCCAAUUGUGGCCAGU	2543
16059	AUGUAUCCGUUAUUGCUAA	893	16059	AUGUAUCCGUUAUUGCUAA	893	16077	UUGAGCUUACGGAAUACAU	2544
16077	ACUAAUGAUACACCCUAC	894	16077	ACUAAUGAUACACCCUAC	894	16095	GUGAGGUGUAUUAUUAUGU	2545
16095	CGGUACUGGGAAACCUAGU	895	16095	CGGUACUGGGAAACCUAGU	895	16113	ACUCAGGUUCCAGUACCG	2546
16113	UUUUAUGAGGCUUAUUA	896	16113	UUUUAUGAGGCUUAUUA	896	16131	UGUACAUAGCCUUAUAAA	2547
16131	ACACCACAUACAGUCUUGC	897	16131	ACACCACAUACAGUCUUGC	897	16149	GCAAGCUGUAUUGUGGUGU	2548
16149	CAGGCUUAGGUGCUUGUG	898	16149	CAGGCUUAGGUGCUUGUG	898	16167	CACAAGCACUACAGCCUG	2549
16167	GUUUUGCAUUAUACAGA	899	16167	GUUUUGCAUUAUACAGA	899	16185	UCUGGAAUUGCAAAUAC	2550
16185	ACUUCACUUCGUUGCGGUG	900	16185	ACUUCACUUCGUUGCGGUG	900	16203	CACCGCAUUGGUGAAGU	2551
16203	GCCUGUAUAGGAGACCAU	901	16203	GCCUGUAUAGGAGACCAU	901	16221	AUGGUCUCCUAAUACAGGC	2552
16221	UUCCUAUGUUGCAAGUGCU	902	16221	UUCCUAUGUUGCAAGUGCU	902	16239	AGCACUUGCAACAUAGGAA	2553
16239	UGCUAUGACCAUGUCAUUU	903	16239	UGCUAUGACCAUGUCAUUU	903	16257	AAUAGACUUGGUAUAGCA	2554
16257	UCAACAUACACAAAUUAG	904	16257	UCAACAUACACAAAUUAG	904	16275	CUAAUUUGUGAUGUUUGA	2555
16275	GUGUUGUCUGUUAUACCCU	905	16275	GUGUUGUCUGUUAUACCCU	905	16293	AGGAAUUAACAGAAACAC	2556
16293	UAUGUUUGCAUAGCCCCAG	906	16293	UAUGUUUGCAUAGCCCCAG	906	16311	CUGGGCAUUGCAAAACAU	2557
16311	GGUUGUGAUGUCACUGAUG	907	16311	GGUUGUGAUGUCACUGAUG	907	16329	CAUCAGUGACAUACAACC	2558
16329	GUGACACAAUCUGUAUCUAG	908	16329	GUGACACAAUCUGUAUCUAG	908	16347	CUAGAUACAGUUGUGUAC	2559
16347	GGAGGUUAGAGCUUAUUAU	909	16347	GGAGGUUAGAGCUUAUUAU	909	16365	AAUAAUAGCUUACCUCC	2560
16365	UGCAAGUACAUAAAGCCUC	910	16365	UGCAAGUACAUAAAGCCUC	910	16383	GAGGCUUUAUGUGACUUGCA	2561
16383	CCCAUUAUUAUCCAUUAU	911	16383	CCCAUUAUUAUCCAUUAU	911	16401	AUAAUGGAAACUAAUUGG	2562
16401	UGUGCUAUGGUCAGGUUU	912	16401	UGUGCUAUGGUCAGGUUU	912	16419	AAACCUGACCAUUAAGCACA	2563
16419	UUUGGUUUUAUACAAAACA	913	16419	UUUGGUUUUAUACAAAACA	913	16437	UGUUUUUGUAUAAACCAA	2564
16437	ACAUGUAGGCGAGUGACA	914	16437	ACAUGUAGGCGAGUGACA	914	16455	UGUCACUGCCUACACAUUG	2565
16455	AAUGUCACUGACUUAUUAUG	915	16455	AAUGUCACUGACUUAUUAUG	915	16473	CAUUGAAGUGUGUACAUU	2566
16473	GCGAUAGCAACAUUGUAUU	916	16473	GCGAUAGCAACAUUGUAUU	916	16491	AAUCACAUUGUUCUACGCG	2567
16491	UGGACUAAUGCUGGCGAUU	917	16491	UGGACUAAUGCUGGCGAUU	917	16509	AUCCGCCAGCAUUAUGCCA	2568
16509	UACAUACUUGCCAAACAUU	918	16509	UACAUACUUGCCAAACAUU	918	16527	AAGUGUUGGCAAGUAUGUA	2569

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16527	UGUACUGAGACUCAGC	919	16527	UGUACUGAGACUCAGC	919	16545	GCUUGAGUCUCAGUACA	2570
16545	CUUUUCGACAGAAACGC	920	16545	CUUUUCGACAGAAACGC	920	16563	GCUUUUCGUCGCGAAAG	2571
16563	CUCAAAGCCACUGAGGAA	921	16563	CUCAAAGCCACUGAGGAA	921	16581	UUUCCUCAGUGGCUUUGAG	2572
16581	ACAUUUAGCGUCAUAUG	922	16581	ACAUUUAGCGUCAUAUG	922	16599	CAUAGACAGCUUAAAUGU	2573
16599	GGUUAUUGCCACUGACGCG	923	16599	GGUUAUUGCCACUGACGCG	923	16617	CGCGUACAGUGGCAAUACC	2574
16617	GAAGUACUCUCUGACAGAG	924	16617	GAAGUACUCUCUGACAGAG	924	16635	CUCUGUCAGAGAGUACUUC	2575
16635	GAGUUGGAAACCUAGAC	925	16635	GAGUUGGAAACCUAGAC	925	16653	CCCAUGAAGAGUCAAUUC	2576
16653	GAGGUUGGAAACCUAGAC	926	16653	GAGGUUGGAAACCUAGAC	926	16671	GUCUAGGUUUUCCAAACCCUC	2577
16671	CCACCAUUGAACAGAAACU	927	16671	CCACCAUUGAACAGAAACU	927	16689	AGUUUCUGUUAUAGGUGG	2578
16689	UAUGUCUUUACUGUUUACC	928	16689	UAUGUCUUUACUGUUUACC	928	16707	GGUAAACCAUAAAGACAU	2579
16707	CGUGUACUAAAAUAGUA	929	16707	CGUGUACUAAAAUAGUA	929	16725	UACUUAUUUAGUUUACAG	2580
16725	AAAGUACAGAUUGGAGAGU	930	16725	AAAGUACAGAUUGGAGAGU	930	16743	ACUCUCCAAUCUGUACUUC	2581
16743	UACACCUUUUAAAAAGGUG	931	16743	UACACCUUUUAAAAAGGUG	931	16761	CACCUUUUCAAAGGUGUA	2582
16761	GACUUAUGGUGAUGCUUUG	932	16761	GACUUAUGGUGAUGCUUUG	932	16779	CAACAGCAUCCAUAGUC	2583
16779	GUGUACAGAGGUACUACGA	933	16779	GUGUACAGAGGUACUACGA	933	16797	UCGUAGUACCUUGUACAC	2584
16797	ACAUACAAGUUUAAUUGUUG	934	16797	ACAUACAAGUUUAAUUGUUG	934	16815	CAACAUUCAAUUGUAGU	2585
16815	GGUGAUUACUUUGUUGUA	935	16815	GGUGAUUACUUUGUUGUA	935	16833	UCAACACAAAGUAAUCACC	2586
16833	ACAUCUACACUUGUAUUGC	936	16833	ACAUCUACACUUGUAUUGC	936	16851	GCAUUAACAGUGUGAGAGU	2587
16851	CCACUUAUGGACCUUACUC	937	16851	CCACUUAUGGACCUUACUC	937	16869	GAGUAGGUGGCACUAGUGG	2588
16869	CUAGUGCCACAAGAGCACU	938	16869	CUAGUGCCACAAGAGCACU	938	16887	AGUGCUUUGUGGCGACUAG	2589
16887	UAUGUGAGAAUUAUUGGCU	939	16887	UAUGUGAGAAUUAUUGGCU	939	16905	AGCCAGUAAUUCACAU	2590
16905	UUGUACCCAAACACUACA	940	16905	UUGUACCCAAACACUACA	940	16923	UGUUGAGUGUUGGUAACA	2591
16923	AUCUCAGAGAGUUUUCUA	941	16923	AUCUCAGAGAGUUUUCUA	941	16941	UAGAAACUACUCUGAGU	2592
16941	AGCAUUGUUGCAAAUUAUC	942	16941	AGCAUUGUUGCAAAUUAUC	942	16959	GAUAAUUGCAACAUUGCU	2593
16959	CAAAAGGUCGCAUGCAAA	943	16959	CAAAAGGUCGCAUGCAAA	943	16977	UUUGCAUGCCGACCUUUG	2594
16977	AAGUACUCUACACUCCAA	944	16977	AAGUACUCUACACUCCAA	944	16995	CUUGGAGUGUAGAGUACUU	2595
16995	GGACCAUUGGUAUUGGUA	945	16995	GGACCAUUGGUAUUGGUA	945	17013	UACCAUACCCAGGUGGUCC	2596
17013	AAGAGUCAUUUUGCCAUUG	946	17013	AAGAGUCAUUUUGCCAUUG	946	17031	CGAUGGCAAAUAGACUUCU	2597
17031	GGACUUGCUCUUAUUAACC	947	17031	GGACUUGCUCUUAUUAACC	947	17049	GGUAAUAGAGAGCAAGUCC	2598
17049	CCAUCUGCUGCAUAGUGU	948	17049	CCAUCUGCUGCAUAGUGU	948	17067	ACACUAGCGAGCAGAGUGG	2599
17067	UAUACGGCAUGCUCUACUG	949	17067	UAUACGGCAUGCUCUACUG	949	17085	CAUGAGAGCAUGCCGUUAU	2600
17085	GCAGCUGUUGAUGCCCUAU	950	17085	GCAGCUGUUGAUGCCCUAU	950	17103	AUAGGGCAUCAAACGUGC	2601
17103	UGUAAAAGGCAUUAUAAU	951	17103	UGUAAAAGGCAUUAUAAU	951	17121	AUUUAAUUGCCUUUUCACA	2602
17121	UAUUUGCCCAUAGUAAAU	952	17121	UAUUUGCCCAUAGUAAAU	952	17139	AUUUAUCUUAUGGCAAAUA	2603
17139	UGUUAUGAAUUAUACCUUG	953	17139	UGUUAUGAAUUAUACCUUG	953	17157	CAGGUUAUUAUUAUUAUA	2604
17157	GCAGCUGCGCGGAGAGU	954	17157	GCAGCUGCGCGGAGAGU	954	17175	ACUUAACGCGCGACGCGC	2605
17175	UGUUUUGAAUUAUUAUAA	955	17175	UGUUUUGAAUUAUUAUAA	955	17193	CUUUGAAUUUAUCAAACA	2606
17193	GUGAAUUAACACUAGAAC	956	17193	GUGAAUUAACACUAGAAC	956	17211	GUUCUAGUGUUAUUAUAC	2607
17211	CAGUUAUUUUCUGCACUG	957	17211	CAGUUAUUUUCUGCACUG	957	17229	CAGUGCAAAACAUACUG	2608
17229	GUAAUUGCAUUGCCAGAAA	958	17229	GUAAUUGCAUUGCCAGAAA	958	17247	UUUCUGGCAUUGCAUUUAC	2609
17247	ACAACUGCUGACAUUGUAG	959	17247	ACAACUGCUGACAUUGUAG	959	17265	CUACAAUGUCAGCAGUUGU	2610
17265	GUCUUUUGAUGAAAUUCUA	960	17265	GUCUUUUGAUGAAAUUCUA	960	17283	UAGAGAUUUCAUCAAAAGAC	2611

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17283	AUGGCUACUAAUUAUGACU	961	17283	AUGGCUACUAAUUAUGACU	961	17301	AGUCAUAAUUAUGAGCCAU	2612
17301	UUGAGUGUUGUCAAGCUA	962	17301	UUGAGUGUUGUCAAGCUA	962	17319	UAGCAUUGACACACUCA	2613
17319	AGACUUGUGGCAAAACACU	963	17319	AGACUUGUGGCAAAACACU	963	17337	AGUGUUUGCAGCAAGUCU	2614
17337	UACGUCUAAUUAUGGCAUC	964	17337	UACGUCUAAUUAUGGCAUC	964	17355	GAUCGCCAAUUAAGACGUA	2615
17355	CCUGCUCAAUUACAGCC	965	17355	CCUGCUCAAUUACAGCC	965	17373	GGCUGGUAUUAUGAGCAGG	2616
17373	CCCGCACAUUUGCUGACUA	966	17373	CCCGCACAUUUGCUGACUA	966	17391	UAGUCAGCAUUGCGGGG	2617
17391	AAAGGCACAUAGAACAG	967	17391	AAAGGCACAUAGAACAG	967	17409	CUGGUUCUAGUGGCUUU	2618
17409	GAUAUUUAUUAUCAGUGU	968	17409	GAUAUUUAUUAUCAGUGU	968	17427	ACACUGAAUUAUUAUUC	2619
17427	UGCAGACUUAUUAAGACAA	969	17427	UGCAGACUUAUUAAGACAA	969	17445	UUGUUUAUUAUUAAGUGCA	2620
17445	AUAGGUCAGACAUUUC	970	17445	AUAGGUCAGACAUUUC	970	17463	GGAACAUGUCUGGACCUAU	2621
17463	CUUGGAACUUGCGCGUU	971	17463	CUUGGAACUUGCGCGUU	971	17481	AACGGCACAAGUUCGCAAG	2622
17481	UGUCCUGGCAUUAUUG	972	17481	UGUCCUGGCAUUAUUG	972	17499	CAACAUAUUGACGAGCA	2623
17499	GACACUGAGUGCUUUAAG	973	17499	GACACUGAGUGCUUUAAG	973	17517	CUAAGCACUCACAGUGUC	2624
17517	GUUAUGACAAUUAAGCUAA	974	17517	GUUAUGACAAUUAAGCUAA	974	17535	UUAGCUUAUUAUUAAGAAAC	2625
17535	AAAGCACACAAGGAUAAU	975	17535	AAAGCACACAAGGAUAAU	975	17553	ACUUAUCCUUGUGUGCUUU	2626
17553	UCAGCUCUAAUUGCUAA	976	17553	UCAGCUCUAAUUGCUAA	976	17571	UUUAGAGCAUUGAGCUGA	2627
17571	AUGUUCUACAAAGGUGUA	977	17571	AUGUUCUACAAAGGUGUA	977	17589	UAACACCUUUGUAGAACAU	2628
17589	AUUAACAUAUUAUUAU	978	17589	AUUAACAUAUUAUUAU	978	17607	UAGAAACAUAUUAUUAU	2629
17607	UCUGCAAUCAACAGACCUC	979	17607	UCUGCAAUCAACAGACCUC	979	17625	GAGGUCUGUUAUUAUUAU	2630
17625	CAAAUAGGCGUUAUUAAG	980	17625	CAAAUAGGCGUUAUUAAG	980	17643	CUCUUAACAAGCCUUAUUAU	2631
17643	GAUUUCUUAACAGCAUUC	981	17643	GAUUUCUUAACAGCAUUC	981	17661	GAUUGCGUGUAAGAAUUAU	2632
17661	CCUGCUUGGAGAAAGCUG	982	17661	CCUGCUUGGAGAAAGCUG	982	17679	CAGCUUUUCUCCAAAGCAGG	2633
17679	GUUUUAUCUACCCUUAUA	983	17679	GUUUUAUCUACCCUUAUA	983	17697	UAUAGGUGAGAUAAUUAU	2634
17697	AAUUCACAAAGCCUGUAG	984	17697	AAUUCACAAAGCCUGUAG	984	17715	CUACAGCGUUCUGUGAAUUA	2635
17715	CGUUCAAAAUUAUUAUUA	985	17715	CGUUCAAAAUUAUUAUUA	985	17733	AUCCUAAAGAUUUUUAAGAGC	2636
17733	UUGCCUACGACAGCUGUUG	986	17733	UUGCCUACGACAGCUGUUG	986	17751	CAACAGUCUGCGUAGGCAA	2637
17751	GAUUAUACAGGCUUUCUG	987	17751	GAUUAUACAGGCUUUCUG	987	17769	CAGAACCUGUGAGUUAUUAU	2638
17769	GAUAUAGCAUUAUUAUUA	988	17769	GAUAUAGCAUUAUUAUUA	988	17787	AUAUGACAUAUUAUUAUUAU	2639
17787	UUCACACAACUUAUUAUUA	989	17787	UUCACACAACUUAUUAUUA	989	17805	UUUCAGUUAUUAUUAUUAU	2640
17805	ACAGCACACUUAUUAUUAU	990	17805	ACAGCACACUUAUUAUUAU	990	17823	CAUUAACAAGUUGUGUGU	2641
17823	GUCAACCGCUUAUUAUUAU	991	17823	GUCAACCGCUUAUUAUUAU	991	17841	CCACAUAAGAGCGUUAUUAU	2642
17841	GUUAUACAAGGCAUUAUUA	992	17841	GUUAUACAAGGCAUUAUUA	992	17859	UUUUUGCCUUAUUAUUAUUA	2643
17859	AUUGGCAUUAUUAUUAUUA	993	17859	AUUGGCAUUAUUAUUAUUA	993	17877	UUUAGCAUUAUUAUUAUUAU	2644
17877	AUGUCUUAUUAUUAUUAUUA	994	17877	AUGUCUUAUUAUUAUUAUUA	994	17895	AAAGUACUUAUUAUUAUUAU	2645
17895	UAUGACAACUUAUUAUUAUUA	995	17895	UAUGACAACUUAUUAUUAUUA	995	17913	UAAAUUGCAGUUAUUAUUAU	2646
17913	ACAAGUCUUAUUAUUAUUAU	996	17913	ACAAGUCUUAUUAUUAUUAU	996	17931	GUGUAUUUAUUAUUAUUAUUA	2647
17931	CGUCGCAUUAUUAUUAUUAU	997	17931	CGUCGCAUUAUUAUUAUUAU	997	17949	AUGUAGCCACAUAUUAUUAUUA	2648
17949	UUAACAAGCAGAAUUAUUAUUA	998	17949	UUAACAAGCAGAAUUAUUAUUA	998	17967	UUAUAUUUAUUAUUAUUAUUA	2649
17967	ACUGGACUUAUUAUUAUUAUUA	999	17967	ACUGGACUUAUUAUUAUUAUUA	999	17985	AGUCCUUAUUAUUAUUAUUAUUA	2650
17985	UGUAUAAGAUUAUUAUUAUUA	1000	17985	UGUAUAAGAUUAUUAUUAUUA	1000	18003	CAGUAUAUUAUUAUUAUUAUUA	2651
18003	GGUCUUAUUAUUAUUAUUAUUA	1001	18003	GGUCUUAUUAUUAUUAUUAUUA	1001	18021	CCUGUUAUUAUUAUUAUUAUUA	2652
18021	GCACCUACACACCUUUAUUAUUA	1002	18021	GCACCUACACACCUUUAUUAUUA	1002	18039	CGCUGAGGUGUGUUAUUAUUAUUA	2653

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18039	GUUGAUUAAAGUUCAAGA	1003	18039	GUUGAUUAAAGUUCAAGA	1003	18057	UCUUGAACUUUAUAUCAAC	2654
18057	ACUGAAGGAUUAUGUGUUG	1004	18057	ACUGAAGGAUUAUGUGUUG	1004	18075	CAACACAUAUCCUUCAGU	2655
18075	GACAUACAGGUAUACCAA	1005	18075	GACAUACAGGUAUACCAA	1005	18093	UUGUAUGCCUGGUUAGUC	2656
18093	AAGGACAUAGACCUACCGUA	1006	18093	AAGGACAUAGACCUACCGUA	1006	18111	UACGGUAGGUCAUGUCCU	2657
18111	AGACUCAUCUUAUGAUGG	1007	18111	AGACUCAUCUUAUGAUGG	1007	18129	CCAUCAUAGAGAUAGUCU	2658
18129	GGUUCAAAUAGAAUUAAC	1008	18129	GGUUCAAAUAGAAUUAAC	1008	18147	GGUAUUCAUUUUGAAACC	2659
18147	CAAGUCAUGGUUACCCUA	1009	18147	CAAGUCAUGGUUACCCUA	1009	18165	UAGGUAACCAUUGACUUG	2660
18165	AUAUGUUUAUACCCCGG	1010	18165	AUAUGUUUAUACCCCGG	1010	18183	CGCGGUGUAUAAACAUAU	2661
18183	GAAGAAGCUAUUCGUCACG	1011	18183	GAAGAAGCUAUUCGUCACG	1011	18201	CGUGACGAUAGCUUCUUC	2662
18201	GUUCGUGCGUGGAUUGGCU	1012	18201	GUUCGUGCGUGGAUUGGCU	1012	18219	AGCCAAUCCACGCACGAAC	2663
18219	UUUGAUAGAGGGCUGUC	1013	18219	UUUGAUAGAGGGCUGUC	1013	18237	GACAGCCUCUACAUCAAA	2664
18237	UAUGCAACUAGAGUUCUG	1014	18237	UAUGCAACUAGAGUUCUG	1014	18255	CAGCAUCUCUAGUUGCAUG	2665
18255	GUGGUAACUACCUACCCUC	1015	18255	GUGGUAACUACCUACCCUC	1015	18273	GAGGUAGGUAGUACCCAC	2666
18273	CUCAGCUAGGAUUUUCUA	1016	18273	CUCAGCUAGGAUUUUCUA	1016	18291	UAGAAAUCUAGCUGGAG	2667
18291	ACAGGUGUUAACUUAUAG	1017	18291	ACAGGUGUUAACUUAUAG	1017	18309	CUACUAAUUUAACACCUUG	2668
18309	GCUGUACCGACUGGUUAUG	1018	18309	GCUGUACCGACUGGUUAUG	1018	18327	CAUACCAUGCGGUACAGC	2669
18327	GUUGACACUGAAAUUAACA	1019	18327	GUUGACACUGAAAUUAACA	1019	18345	UGUUAUUUCAGUGUACAAC	2670
18345	ACAGAAUCCACGAGUUA	1020	18345	ACAGAAUCCACGAGUUA	1020	18363	UAACUCUGGUGAAUUCUGU	2671
18363	AAUGCAAAACCUCCACAC	1021	18363	AAUGCAAAACCUCCACAC	1021	18381	CUGGUGGAGGUUUUGCAUU	2672
18381	GGUGACCAUUAUUAACAUC	1022	18381	GGUGACCAUUAUUAACAUC	1022	18399	GAUGUUUAACUUGUACAC	2673
18399	CUUAUACCAUCUUAUUAUA	1023	18399	CUUAUACCAUCUUAUUAUA	1023	18417	UAUUAUUAUGGUGUAUAG	2674
18417	AAAGGUUGCCUGGAUUG	1024	18417	AAAGGUUGCCUGGAUUG	1024	18435	CAUUCGAGGGCAAGCCUUU	2675
18435	GUAGUGCGUAUUAAGAUAG	1025	18435	GUAGUGCGUAUUAAGAUAG	1025	18453	CUACUUAUAUCGCACUAC	2676
18453	GUACAAUUGCUCAGUGUAU	1026	18453	GUACAAUUGCUCAGUGUAU	1026	18471	UAUCACUGAGCAUUUUGUAC	2677
18471	ACACUGAAAGGAUUGUCAG	1027	18471	ACACUGAAAGGAUUGUCAG	1027	18489	CUGACAAUCCUUCAGUGU	2678
18489	GACAGAGUCGUGUUCGUCC	1028	18489	GACAGAGUCGUGUUCGUCC	1028	18507	GGACGAACACGACUCUGUC	2679
18507	CUUUGGCGCAUGGCUUUG	1029	18507	CUUUGGCGCAUGGCUUUG	1029	18525	CAAAGCAUGCGCCCAAG	2680
18525	GAGCUUACAUAUUAAGU	1030	18525	GAGCUUACAUAUUAAGU	1030	18543	ACUUAUUGAUUGUAAGCUC	2681
18543	UACUUUGUAAGAUUGGAC	1031	18543	UACUUUGUAAGAUUGGAC	1031	18561	GUCCAAUUCUUGACAAAGUA	2682
18561	CCUGAAAGAACGUGUUGUC	1032	18561	CCUGAAAGAACGUGUUGUC	1032	18579	GACAACACGUGUUCACAGG	2683
18579	CUGUGAGACAAACGUGCAA	1033	18579	CUGUGAGACAAACGUGCAA	1033	18597	UUGCACGUUUGUCACACAG	2684
18597	ACUUGCUUUUCUACUUAU	1034	18597	ACUUGCUUUUCUACUUAU	1034	18615	AUGAAGUAGAAAAGCAAGU	2685
18615	UCAGAUACUUAUUGCCUGCU	1035	18615	UCAGAUACUUAUUGCCUGCU	1035	18633	AGCAGGCAUAAAGUACUGA	2686
18633	UGGAUACUUAUCUGUGGCU	1036	18633	UGGAUACUUAUCUGUGGCU	1036	18651	AACCCACAGAAUUGAUUCCA	2687
18651	UUUGACUUAUGUCUAUUAAC	1037	18651	UUUGACUUAUGUCUAUUAAC	1037	18669	GGUUAUAGACAUAGUCAA	2688
18669	CCAUAUUAUGAUUGAUUUC	1038	18669	CCAUAUUAUGAUUGAUUUC	1038	18687	GACAUAUUAUUAUUAUUG	2689
18687	CAGUAGUGGGGUUAUACCG	1039	18687	CAGUAGUGGGGUUAUACCG	1039	18705	CCGUAAGCCCAUUGCUGU	2690
18705	GGUAACCUUACAGAUUAAC	1040	18705	GGUAACCUUACAGAUUAAC	1040	18723	GGUUAUCUGAAGGUUAAC	2691
18723	CAUGACCAACAUUGCCAGG	1041	18723	CAUGACCAACAUUGCCAGG	1041	18741	CCUGGCAUUGUUGGUCAUG	2692
18741	GUACAUUGGAAUUGCACAUG	1042	18741	GUACAUUGGAAUUGCACAUG	1042	18759	CAUGUGCAUUAUCCAUUAC	2693
18759	GUGGCUAGUUGUAGUUCUA	1043	18759	GUGGCUAGUUGUAGUUCUA	1043	18777	UAGCAUACAAUAGCCAC	2694
18777	AUCAUGACUAGAUUUUAG	1044	18777	AUCAUGACUAGAUUUUAG	1044	18795	CUAAACAUCUAGUUAUAG	2695

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18795	GCAGUCCAUGAGUGCUUUG	1045	18795	GCAGUCCAUGAGUGCUUUG	1045	18813	CAAAGCACUUGGACUGC	2696
18813	GUUAGCGGUUUAUUGGU	1046	18813	GUUAGCGGUUUAUUGGU	1046	18831	ACCAUCAAAGCGCUUAAAC	2697
18831	UCUGUUUAAUACCCUAUUA	1047	18831	UCUGUUUAAUACCCUAUUA	1047	18849	UAAUAGGUAUUAACAAGA	2698
18849	AUAGGAGUAUAACUGAGGG	1048	18849	AUAGGAGUAUAACUGAGGG	1048	18867	CCUCAGUUAUUAUUAUUA	2699
18867	GUUAAUUCUGCUUGCAGAA	1049	18867	GUUAAUUCUGCUUGCAGAA	1049	18885	UUCUGCAAGCAGAAUUAAC	2700
18885	AAAGUACAACACAUUGGUUG	1050	18885	AAAGUACAACACAUUGGUUG	1050	18903	CAACCAUGUGUUAUUAUUA	2701
18903	GUGAAGUCUGCAUUGCUUG	1051	18903	GUGAAGUCUGCAUUGCUUG	1051	18921	CAAGCAUUGGACAUUAUUA	2702
18921	GUUGAUAAGUUUCCAGUUC	1052	18921	GUUGAUAAGUUUCCAGUUC	1052	18939	GAAGGAAACAUUAUUAUUA	2703
18939	CUUAGACAUUUGGAAUUA	1053	18939	CUUAGACAUUUGGAAUUA	1053	18957	GAUUCCAAUGUCAUUAUUA	2704
18957	CCAAAGGCUAUAAGUGUG	1054	18957	CCAAAGGCUAUAAGUGUG	1054	18975	CACACUUAUUAAGCUGG	2705
18975	GUGCCUCAGGCUAAGUAG	1055	18975	GUGCCUCAGGCUAAGUAG	1055	18993	CUACUUCAGCUGAGGAC	2706
18993	GAUUGGAAUUAUUAUUA	1056	18993	GAUUGGAAUUAUUAUUA	1056	19011	CAUCGUAGAAUUAUUAUUA	2707
19011	GCUCAGCCAUUAUUAUUA	1057	19011	GCUCAGCCAUUAUUAUUA	1057	19029	UGUCACUUAUUAUUAUUA	2708
19029	AAAGCUUAUUAUUAUUA	1058	19029	AAAGCUUAUUAUUAUUA	1058	19047	CCUCUAUUAUUAUUAUUA	2709
19047	GAACUCUUAUUAUUAUUA	1059	19047	GAACUCUUAUUAUUAUUA	1059	19065	CAUAAGAAUUAUUAUUAUUA	2710
19065	GUACACAUUAUUAUUAUUA	1060	19065	GUACACAUUAUUAUUAUUA	1060	19083	AUUUAUGGUAUUAUUAUUA	2711
19083	UUCACUUAUUAUUAUUAUUA	1061	19083	UUCACUUAUUAUUAUUAUUA	1061	19101	AACAAACCAUUAUUAUUA	2712
19101	UUGUUAUUAUUAUUAUUA	1062	19101	UUGUUAUUAUUAUUAUUA	1062	19119	CGUUAUUAUUAUUAUUA	2713
19119	GUUGAUCGUUAUUAUUAUUA	1063	19119	GUUGAUCGUUAUUAUUAUUA	1063	19137	UGGCUUGGUAUUAUUAUUA	2714
19137	AUUGCAUUAUUAUUAUUAUUA	1064	19137	AUUGCAUUAUUAUUAUUAUUA	1064	19155	ACCUACACAUUAUUAUUAUUA	2715
19155	UUUGACACAAGAGUCUUAUUA	1065	19155	UUUGACACAAGAGUCUUAUUA	1065	19173	ACAAGACUUAUUAUUAUUA	2716
19173	UCAACUUAUUAUUAUUAUUA	1066	19173	UCAACUUAUUAUUAUUAUUA	1066	19191	CUGGUAUUAUUAUUAUUA	2717
19191	GGCUGUAUUAUUAUUAUUAUUA	1067	19191	GGCUGUAUUAUUAUUAUUAUUA	1067	19209	AACUACCAUUAUUAUUAUUA	2718
19209	UUGUAUUAUUAUUAUUAUUA	1068	19209	UUGUAUUAUUAUUAUUAUUA	1068	19227	CAUCUUAUUAUUAUUAUUA	2719
19227	GCAUUAUUAUUAUUAUUAUUA	1069	19227	GCAUUAUUAUUAUUAUUAUUA	1069	19245	AAGCUGGAGUGGUAUUAUUA	2720
19245	UUCGAUUAUUAUUAUUAUUA	1070	19245	UUCGAUUAUUAUUAUUAUUA	1070	19263	UAAUUGCACAUUAUUAUUA	2721
19263	ACUAAUUAUUAUUAUUAUUA	1071	19263	ACUAAUUAUUAUUAUUAUUA	1071	19281	GCAUUAUUAUUAUUAUUAUUA	2722
19281	CCUUAUUAUUAUUAUUAUUA	1072	19281	CCUUAUUAUUAUUAUUAUUA	1072	19299	CAGAAUUAUUAUUAUUAUUA	2723
19299	GAUAGUUAUUAUUAUUAUUA	1073	19299	GAUAGUUAUUAUUAUUAUUA	1073	19317	GAGACUUAUUAUUAUUAUUA	2724
19317	CAUGGCAUUAUUAUUAUUAUUA	1074	19317	CAUGGCAUUAUUAUUAUUAUUA	1074	19335	ACACUUAUUAUUAUUAUUA	2725
19335	UCGGAUUAUUAUUAUUAUUA	1075	19335	UCGGAUUAUUAUUAUUAUUA	1075	19353	GAACAUAUUAUUAUUAUUA	2726
19353	CCACUUAUUAUUAUUAUUAUUA	1076	19353	CCACUUAUUAUUAUUAUUAUUA	1076	19371	ACGUAUUAUUAUUAUUAUUA	2727
19371	UGUAUUAUUAUUAUUAUUAUUA	1077	19371	UGUAUUAUUAUUAUUAUUAUUA	1077	19389	AUUAUUAUUAUUAUUAUUA	2728
19389	UUAGUUAUUAUUAUUAUUAUUA	1078	19389	UUAGUUAUUAUUAUUAUUAUUA	1078	19407	UGCAAACAGCACCACCUAA	2729
19407	UAGACCAUUAUUAUUAUUAUUA	1079	19407	UAGACCAUUAUUAUUAUUAUUA	1079	19425	ACUUAUUAUUAUUAUUAUUA	2730
19425	UACCGACAUUAUUAUUAUUAUUA	1080	19425	UACCGACAUUAUUAUUAUUAUUA	1080	19443	CAUCAAUUAUUAUUAUUAUUA	2731
19443	GCAUUAUUAUUAUUAUUAUUA	1081	19443	GCAUUAUUAUUAUUAUUAUUA	1081	19461	AAUUAUUAUUAUUAUUAUUA	2732
19461	UCUGCUGGUAUUAUUAUUAUUA	1082	19461	UCUGCUGGUAUUAUUAUUAUUA	1082	19479	AUAGGCUAAUUAUUAUUAUUA	2733
19479	UGGAUUAUUAUUAUUAUUAUUA	1083	19479	UGGAUUAUUAUUAUUAUUAUUA	1083	19497	CAAAUUAUUAUUAUUAUUA	2734
19497	GAUACUUAUUAUUAUUAUUAUUA	1084	19497	GAUACUUAUUAUUAUUAUUAUUA	1084	19515	UCCACAGGUUAUUAUUAUUA	2735
19515	AAUUAUUAUUAUUAUUAUUAUUA	1085	19515	AAUUAUUAUUAUUAUUAUUAUUA	1085	19533	GUAAUUAUUAUUAUUAUUAUUA	2736
19533	CAGAUUAUUAUUAUUAUUAUUA	1086	19533	CAGAUUAUUAUUAUUAUUAUUA	1086	19551	CCACAUAUUAUUAUUAUUAUUA	2737

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19551	GCUUUAUUGUUAUUA	1087	19551	GCUUUAUUGUUAUUA	1087	19569	UAUUAACAACAUUAAGC	2738
19569	AAAGGACACUUAUGGAC	1088	19569	AAAGGACACUUAUGGAC	1088	19587	GUCCAUAAGUGUCCUUA	2739
19587	CACGCGGCGAAGCACCUG	1089	19587	CACGCGGCGAAGCACCUG	1089	19605	CAGGUGCUUGCGCGGCGUG	2740
19605	GUUCCAUCAUUAUUAUG	1090	19605	GUUCCAUCAUUAUUAUG	1090	19623	CAUUAUAUUGAUAACAC	2741
19623	GUUUAUACAACAAAGGUAG	1091	19623	GUUUAUACAACAAAGGUAG	1091	19641	CUACCUUUGUGUAACACG	2742
19641	GAUGGUUAUGAUGGAGA	1092	19641	GAUGGUUAUGAUGGAGA	1092	19659	UCUCCACAUAUACCAUC	2743
19659	AUCUUUGAAAUUAAAGACAA	1093	19659	AUCUUUGAAAUUAAAGACAA	1093	19677	UUGUCUUAUUAUUAAGAU	2744
19677	ACACUCCUGUUAUUAUGU	1094	19677	ACACUCCUGUUAUUAUGU	1094	19695	CAACAUUAACAGGAAGUGU	2745
19695	GCAUUGAGCUUUGGCUA	1095	19695	GCAUUGAGCUUUGGCUA	1095	19713	UAGCCCAAAGCUCAAAUGC	2746
19713	AAGCGUAACAUUAACACAG	1096	19713	AAGCGUAACAUUAACACAG	1096	19731	CUGGUUAUUAUGUAAGCUU	2747
19731	GUGCCAGAGAUUAAGAUAC	1097	19731	GUGCCAGAGAUUAAGAUAC	1097	19749	GUUUCUUAUUAUCUGGCAC	2748
19749	CUCAAUUAUUGGGUGUUG	1098	19749	CUCAAUUAUUGGGUGUUG	1098	19767	CAACACCCAAUUAUUAUG	2749
19767	GAUUAUCGUCUAUAUACUG	1099	19767	GAUUAUCGUCUAUAUACUG	1099	19785	CAGUAUUAAGCAGGAUAUC	2750
19785	GUUAUCUGGGACUACAAA	1100	19785	GUUAUCUGGGACUACAAA	1100	19803	UUUUGUAGCCGAGAUUAC	2751
19803	AGAGAAAGCCCGACACAU	1101	19803	AGAGAAAGCCCGACACAU	1101	19821	CAUGUGCUGGGCUUCUCU	2752
19821	GUUUAUUAUUGGGUGUCU	1102	19821	GUUUAUUAUUGGGUGUCU	1102	19839	AGACACCUUAUUGAUAUC	2753
19839	UGCAAAUAGCUGACAUUG	1103	19839	UGCAAAUAGCUGACAUUG	1103	19857	CAUUGCAGUAUUAUGGCA	2754
19857	GCCAAAGAACCUACUGAGA	1104	19857	GCCAAAGAACCUACUGAGA	1104	19875	UCUCAGUAGGUUUCUUGGC	2755
19875	AGUGCUUUGUUCUACUUA	1105	19875	AGUGCUUUGUUCUACUUA	1105	19893	UAAGUGAAGAACCAAGCACU	2756
19893	ACUGUCUUGUUAUGGUA	1106	19893	ACUGUCUUGUUAUGGUA	1106	19911	UACCAUAACCAAGACAGU	2757
19911	AGAGUGGAAGGACAGGUAG	1107	19911	AGAGUGGAAGGACAGGUAG	1107	19929	CAUUGCUGUUAUUAUUAUG	2758
19929	GACCUUUUUAAGAAAGCCG	1108	19929	GACCUUUUUAAGAAAGCCG	1108	19947	GGCGUUAUUAUUAUUAUG	2759
19947	CGUUAUGGUUUAUUAUUA	1109	19947	CGUUAUGGUUUAUUAUUA	1109	19965	UUAUUAUUAUUAUUAUUA	2760
19965	ACAGAAAGGUUUAUUAUUA	1110	19965	ACAGAAAGGUUUAUUAUUA	1110	19983	CUUUGACUGAACCUUCUGU	2761
19983	GGUUAACACCUUAUUAUUA	1111	19983	GGUUAACACCUUAUUAUUA	1111	20001	CCUUUGAAGGUUAUUAUUA	2762
20001	GGACAGCAAGCUAGCG	1112	20001	GGACAGCAAGCUAGCG	1112	20019	CGCUAGCUUUGCUGGUGC	2763
20019	GUCAUUGGAGUCACAUUA	1113	20019	GUCAUUGGAGUCACAUUA	1113	20037	UUAUUGGAGUCACAUUA	2764
20037	AUUGGAGAAUCAGUAAAA	1114	20037	AUUGGAGAAUCAGUAAAA	1114	20055	UUUUUACUGAUUUAUUAUUA	2765
20055	ACACAGUUUAUUAUUAUUA	1115	20055	ACACAGUUUAUUAUUAUUA	1115	20073	UAAAGUUAUUAUUAUUAUUA	2766
20073	AAGAAAGUAGCGCAUUA	1116	20073	AAGAAAGUAGCGCAUUA	1116	20091	UAAUGCGUUAUUAUUAUUA	2767
20091	AUUAACAGUUGCCUGAAA	1117	20091	AUUAACAGUUGCCUGAAA	1117	20109	UUUCAGGCAACUGUUAUUA	2768
20109	ACCUACUUUACUCAGAGCA	1118	20109	ACCUACUUUACUCAGAGCA	1118	20127	UGCUCUGAGUUAUUAUUA	2769
20127	AGAGACUUUAGGAAUUAUUA	1119	20127	AGAGACUUUAGGAAUUAUUA	1119	20145	UAAAUUCCUUAUUAUUAUUA	2770
20145	AAGCCAGAUUUAUUAUUAUUA	1120	20145	AAGCCAGAUUUAUUAUUAUUA	1120	20163	CCAUUUGUUAUUAUUAUUAUUA	2771
20163	GAACUGACUUUUCUGGAGC	1121	20163	GAACUGACUUUUCUGGAGC	1121	20181	GCUCGAGAAAGUUAUUAUUA	2772
20181	CUCGCUUUGGAAUUAUUA	1122	20181	CUCGCUUUGGAAUUAUUA	1122	20199	UGAAUUAUUAUUAUUAUUA	2773
20199	AUACAGCGAUUAUUAUUAUUA	1123	20199	AUACAGCGAUUAUUAUUAUUA	1123	20217	CGAGCUUUAUUAUUAUUAUUA	2774
20217	GAGGCUUUAUUAUUAUUAUUA	1124	20217	GAGGCUUUAUUAUUAUUAUUA	1124	20235	GUUCGAGGCAUUAUUAUUAUUA	2775
20235	CACAGCUUUAUUAUUAUUAUUA	1125	20235	CACAGCUUUAUUAUUAUUAUUA	1125	20253	AUUCGCUUUAUUAUUAUUAUUA	2776
20253	UUCAGCUUUAUUAUUAUUAUUA	1126	20253	UUCAGCUUUAUUAUUAUUAUUA	1126	20271	CAAGUUGUUAUUAUUAUUAUUA	2777
20271	GGCGGCUUUAUUAUUAUUAUUA	1127	20271	GGCGGCUUUAUUAUUAUUAUUA	1127	20289	UCAUUAUUAUUAUUAUUAUUA	2778
20289	AUAGGCUUUAUUAUUAUUAUUA	1128	20289	AUAGGCUUUAUUAUUAUUAUUA	1128	20307	AGCGCUUUAUUAUUAUUAUUA	2779

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20307	UCACAAGAUUACCCACUUA	1129	20307	UCACAAGAUUACCCACUUA	1129	20325	UAAUGGUGAAUUCUUGUGA	2780
20325	AAUUAAGAGAUUUUAUCC	1130	20325	AAUUAAGAGAUUUUAUCC	1130	20343	GGAAAAUCCUCUAAUUU	2781
20343	CCUUAUGGACAGCAGUGA	1131	20343	CCUUAUGGACAGCAGUGA	1131	20361	UCACUGGUGUCCAUAGG	2782
20361	AAAAUUACUUAUACAG	1132	20361	AAAAUUACUUAUACAG	1132	20379	CUGUUAUGAAGUAAUUUU	2783
20379	GAUGCGCAACAGGUUCAU	1133	20379	GAUGCGCAACAGGUUCAU	1133	20397	AGAAACCCUGUUUGCGCAUC	2784
20397	UCAAUAUGUGUUGUUCUG	1134	20397	UCAAUAUGUGUUGUUCUG	1134	20415	CAGAACACAGCAUUUUGA	2785
20415	GUGAUUGAUUUUAUUCUG	1135	20415	GUGAUUGAUUUUAUUCUG	1135	20433	CAGUAAAAAGAUCAUAC	2786
20433	GAUGACUUUGUCGAGAUAA	1136	20433	GAUGACUUUGUCGAGAUAA	1136	20451	UUAUCUCGACAAAGUCAUC	2787
20451	AUAAAGUCACAAGAUUUUGU	1137	20451	AUAAAGUCACAAGAUUUUGU	1137	20469	ACAAUUCUUGUGACUUUAU	2788
20469	UCAGUGAUUUCAAAAUGGG	1138	20469	UCAGUGAUUUCAAAAUGGG	1138	20487	CCACUUUUGAAUACACUGA	2789
20487	GUCAAGGUUAUAAUUGACU	1139	20487	GUCAAGGUUAUAAUUGACU	1139	20505	AGUCAUUUGUAAACCUUGAC	2790
20505	UAUGCUGAAUUUAUUAUUA	1140	20505	UAUGCUGAAUUUAUUAUUA	1140	20523	UGAAUGAAUUUCAGCAUA	2791
20523	AUGCUUUGGUGUAAAGGAG	1141	20523	AUGCUUUGGUGUAAAGGAG	1141	20541	CAUCCUUACACCAAAAGCAU	2792
20541	GGACAUGUUGAAACCUUCU	1142	20541	GGACAUGUUGAAACCUUCU	1142	20559	AGAAGUUUCAAACAUUCC	2793
20559	UACCCAAAACUACAAGCAA	1143	20559	UACCCAAAACUACAAGCAA	1143	20577	UUGCUUGUAGUUUUGGGUA	2794
20577	AGUCGAGCGUGGCAACAG	1144	20577	AGUCGAGCGUGGCAACAG	1144	20595	CUGUUGCCACGCGUCGACU	2795
20595	GGUGUUGCGAUGCCUAACU	1145	20595	GGUGUUGCGAUGCCUAACU	1145	20613	AGUAGGCAUCGCAACACC	2796
20613	UUGUACAAGAUCAAAGAA	1146	20613	UUGUACAAGAUCAAAGAA	1146	20631	UUCUUUGCAUCUUUGUACAA	2797
20631	AUGCUUUGUAAAAGUGUG	1147	20631	AUGCUUUGUAAAAGUGUG	1147	20649	CACACUUUCAAAGAAGCAU	2798
20649	GACCUUCAGAAUUUAUGGUG	1148	20649	GACCUUCAGAAUUUAUGGUG	1148	20667	CACCAUAAUUCUGAAGGUC	2799
20667	GAAAUGCUGUUAUACCAA	1149	20667	GAAAUGCUGUUAUACCAA	1149	20685	UUGGUAAACAGCAUUUUC	2800
20685	AAAGGAUUAUUGAUGAAUG	1150	20685	AAAGGAUUAUUGAUGAAUG	1150	20703	CAUUCAGCAUUUAUCCUUU	2801
20703	GUGGCAAAUAUACUAC	1151	20703	GUGGCAAAUAUACUAC	1151	20721	GUUGCAUUAUUCGCGAC	2802
20721	CUGUGCAUUAUUAUUA	1152	20721	CUGUGCAUUAUUAUUA	1152	20739	UAUUUAAGUUAUUGACACAG	2803
20739	ACACUUAUUUAGCUGUAC	1153	20739	ACACUUAUUUAGCUGUAC	1153	20757	GUACAGCUAAAAGUAGUGU	2804
20757	CCCUACAACAUAGAGUUA	1154	20757	CCCUACAACAUAGAGUUA	1154	20775	UAACUCUCAUUGUAGG	2805
20775	AUUCACUUUGGUGUGGCU	1155	20775	AUUCACUUUGGUGUGGCU	1155	20793	AGCCAGCACCACAAAGUAAU	2806
20793	UCUGAUAAGGAGUUGCAC	1156	20793	UCUGAUAAGGAGUUGCAC	1156	20811	GUGCAACUCCUUUAUCAGA	2807
20811	CCAGGUACAGCUGUGCUCA	1157	20811	CCAGGUACAGCUGUGCUCA	1157	20829	UGAGCACAGCUGUACCGG	2808
20829	AGACAAUGGUUGCCCAACUG	1158	20829	AGACAAUGGUUGCCCAACUG	1158	20847	CAGUUGGCAACCAUUGUCU	2809
20847	GGCACACUACUUGUCGAUU	1159	20847	GGCACACUACUUGUCGAUU	1159	20865	AUUCGACAAAGUAGUGGCC	2810
20865	UCAGAUUUUAUAGAUUUG	1160	20865	UCAGAUUUUAUAGAUUUG	1160	20883	CGAAGUCAUUAAGAUUGA	2811
20883	GUCUCCGACGCAUUAUUA	1161	20883	GUCUCCGACGCAUUAUUA	1161	20901	UAGAAUUAUGCUGCGGAGC	2812
20901	ACUUUAUUUGGAGACUGUG	1162	20901	ACUUUAUUUGGAGACUGUG	1162	20919	CACAGUCUCCAAUUUAAGU	2813
20919	GCAACAGUACUACGGCUA	1163	20919	GCAACAGUACUACGGCUA	1163	20937	UAGCCGUUAUGUACUUGGC	2814
20937	AAUAAUUGGACCUUAUUA	1164	20937	AAUAAUUGGACCUUAUUA	1164	20955	UAUAAGGUGCCAUUUUAU	2815
20955	AUUAGCGAUUAUGUAGACC	1165	20955	AUUAGCGAUUAUGUAGACC	1165	20973	GGUCAUACAUAUGCGUAAU	2816
20973	CCUAGGACCAACAUGUGA	1166	20973	CCUAGGACCAACAUGUGA	1166	20991	UCACAUUUUUGGCCUAGG	2817
20991	ACAAAAGAGAAUAGACUCUA	1167	20991	ACAAAAGAGAAUAGACUCUA	1167	21009	UAGAGUCAUUCUCUUUUUGU	2818
21009	AAAGAGGGUUUUUACACUU	1168	21009	AAAGAGGGUUUUUACACUU	1168	21027	AAGUAAAAACCCUUCUUU	2819
21027	UAUCUGUGUGGAUUUAUA	1169	21027	UAUCUGUGUGGAUUUAUA	1169	21045	UUUAUAAUCCACACAGUA	2820
21045	AAGCAAAAACUAGCCUUGG	1170	21045	AAGCAAAAACUAGCCUUGG	1170	21063	CCAGGGCUAGUUUUUGCUU	2821

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21063	GGUGGUUUAUAGCUGUAA	1171	21063	GGUGGUUUAUAGCUGUAA	1171	21081	UUACAGCUUAUAGAACCCACC	2822
21081	AAGAUAAACAGAGCAUUCUU	1172	21081	AAGAUAAACAGAGCAUUCUU	1172	21099	AAGAAUGCUCUGUUAUUCUU	2823
21099	UGGAAUGCUGAGCCUUUACA	1173	21099	UGGAAUGCUGAGCCUUUACA	1173	21117	UGUAAAGGUGCAGCAUUCUA	2824
21117	AAGCUUAUGGGCCAUUUCU	1174	21117	AAGCUUAUGGGCCAUUUCU	1174	21135	AGAAAUGGCCCAUAAAGCUU	2825
21135	UUAUGGUGGACGCUUUUG	1175	21135	UUAUGGUGGACGCUUUUG	1175	21153	CAAAAGCUGCCACCACGAU	2826
21153	GUUACAAUUAUUAUUGCAU	1176	21153	GUUACAAUUAUUAUUGCAU	1176	21171	AUGCAUUUACAUUUGUAA	2827
21171	UCAUCAUGGAAGCAUUAU	1177	21171	UCAUCAUGGAAGCAUUAU	1177	21189	AAAUGCUUCCGGAUGAUGA	2828
21189	UUAUUUGGGCUAACUAUC	1178	21189	UUAUUUGGGCUAACUAUC	1178	21207	GAUAGUUAAGCCCAUUAUA	2829
21207	CUUGGCAAGCCGAAGGAAC	1179	21207	CUUGGCAAGCCGAAGGAAC	1179	21225	GUUCUUCGGCUUGCCCAAG	2830
21225	CAAAUUGAGGCUUAUACCA	1180	21225	CAAAUUGAGGCUUAUACCA	1180	21243	UGGUUAUAGCCAUCAUUAUG	2831
21243	AUGCAUGCUAACUAUUAU	1181	21243	AUGCAUGCUAACUAUUAU	1181	21261	AAUGUAGUUAAGCAUGCAU	2832
21261	UUCUGGAGGAACACAAUUC	1182	21261	UUCUGGAGGAACACAAUUC	1182	21279	GAUUUGUGUUCUCCAGAA	2833
21279	CCUAUCCAGUUGUCUUCU	1183	21279	CCUAUCCAGUUGUCUUCU	1183	21297	AGGAAGACAACUGGUAUAGG	2834
21297	UAUUCACUCUUAUGACAUGA	1184	21297	UAUUCACUCUUAUGACAUGA	1184	21315	UCAUGUCAAAGAGGUAUA	2835
21315	AGCAAUUUCUUAUUAU	1185	21315	AGCAAUUUCUUAUUAU	1185	21333	AUUUAAGAGAAUUAUUGCU	2836
21333	UUAAGAGGAACUGCUGUAA	1186	21333	UUAAGAGGAACUGCUGUAA	1186	21351	UUACAGCAGUUCUUCUUA	2837
21351	AUGUCUCUUAAGGAGAAUC	1187	21351	AUGUCUCUUAAGGAGAAUC	1187	21369	GAUUCUCCUUAAGAGACAU	2838
21369	CAAAUCAUUAUUAUUAU	1188	21369	CAAAUCAUUAUUAUUAU	1188	21387	AAAUCAUAUUAUUAUUAU	2839
21387	UAUUCUCUUCUGGAAUAA	1189	21387	UAUUCUCUUCUGGAAUAA	1189	21405	CUUUUCCAGAAAGAGAAUA	2840
21405	GGUAGGCUUAUUAUUAU	1190	21405	GGUAGGCUUAUUAUUAU	1190	21423	CUCUUAUGAUAAAGCCUACC	2841
21423	GAACAACAAGAGUUGUGG	1191	21423	GAACAACAAGAGUUGUGG	1191	21441	CCACAACUCUGUUAUUAU	2842
21441	GUUUAAGUAUUAUUAU	1192	21441	GUUUAAGUAUUAUUAU	1192	21459	CAAGAAUUAUUAUUAUUAU	2843
21459	GUUUAACAUAUUAUUAU	1193	21459	GUUUAACAUAUUAUUAU	1193	21477	UGUUGGUUAUUAUUAUUAU	2844
21477	GUUUAUAUUAUUAUUAU	1194	21477	GUUUAUAUUAUUAUUAU	1194	21495	AUAUAAGAAUUAUUAUUAU	2845
21495	UUUUUAUUAUUAUUAU	1195	21495	UUUUUAUUAUUAUUAU	1195	21513	CACUAGUGAGAGUAAGAA	2846
21513	GGUAGUGACCUUAGCCGGU	1196	21513	GGUAGUGACCUUAGCCGGU	1196	21531	ACGGGUCAAAGGUCACUACC	2847
21531	UGCACCAUUAUUAUUAU	1197	21531	UGCACCAUUAUUAUUAU	1197	21549	CAUCAUCAAAGUGGUGCA	2848
21549	GUUUAAGCUCUUAUUAU	1198	21549	GUUUAAGCUCUUAUUAU	1198	21567	UGUAAUUAAGGAGCUUGAAC	2849
21567	ACUCAACAUAUUAUUAU	1199	21567	ACUCAACAUAUUAUUAU	1199	21585	UAGAUAAUUAUUAUUAU	2850
21585	AUGAGGGGUUAUUAUUAU	1200	21585	AUGAGGGGUUAUUAUUAU	1200	21603	GAUAGUAAACCCUUAUUAU	2851
21603	CCUGAUGAAUUAUUAUUAU	1201	21603	CCUGAUGAAUUAUUAUUAU	1201	21621	AUCUAAAUUAUUAUUAUUAU	2852
21621	UCAGACACUUAUUAUUAU	1202	21621	UCAGACACUUAUUAUUAU	1202	21639	UUAAUUAAGAGUGUGUGA	2853
21639	ACUCAGGAAUUAUUAUUAU	1203	21639	ACUCAGGAAUUAUUAUUAU	1203	21657	GAAGAAUUAUUAUUAUUAU	2854
21657	CCAUUUUAUUAUUAUUAU	1204	21657	CCAUUUUAUUAUUAUUAU	1204	21675	UAAUUAUUAUUAUUAUUAU	2855
21675	ACAGGGUUUAUUAUUAUUAU	1205	21675	ACAGGGUUUAUUAUUAUUAU	1205	21693	UAAUUAUUAUUAUUAUUAU	2856
21693	AAUCAAGGUUAUUAUUAUUAU	1206	21693	AAUCAAGGUUAUUAUUAUUAU	1206	21711	GGUUGCCAAACGUUAUUAU	2857
21711	CCUGUCAUUAUUAUUAUUAU	1207	21711	CCUGUCAUUAUUAUUAUUAU	1207	21729	CCUUAAGGUAUUAUUAUUAU	2858
21729	GAUGGUAUUAUUAUUAUUAU	1208	21729	GAUGGUAUUAUUAUUAUUAU	1208	21747	CAGCAAAUUAUUAUUAUUAU	2859
21747	GCCACAGAAUUAUUAUUAU	1209	21747	GCCACAGAAUUAUUAUUAU	1209	21765	CAUUUAUUAUUAUUAUUAU	2860
21765	GUUUGCCGUGGUUGGUUU	1210	21765	GUUUGCCGUGGUUGGUUU	1210	21783	AAACCAACCCGAGCAAC	2861
21783	UUUGGUUUAUUAUUAUUAU	1211	21783	UUUGGUUUAUUAUUAUUAU	1211	21801	UGUUAUUAUUAUUAUUAU	2862
21801	AAUUAUUAUUAUUAUUAU	1212	21801	AAUUAUUAUUAUUAUUAU	1212	21819	UCACCGACUGAGCUUGUU	2863

21819	AUUUUUUUUAAACAAUUCUA	1213	21819	AUUUUUUUUAAACAAUUCUA	1213	21837	UAGAAUUGUUUAAUAAUAAU	2864
21837	ACUAAUGUUUGUUUAUACGAG	1214	21837	ACUAAUGUUUGUUUAUACGAG	1214	21855	CUCGUAAACAAACAUUAGU	2865
21855	GCAUGUAACUUUGAAUUGU	1215	21855	GCAUGUAACUUUGAAUUGU	1215	21873	ACAAUUCAAAGUUUAACAGC	2866
21873	UGUGACAACCCUUUCUUUG	1216	21873	UGUGACAACCCUUUCUUUG	1216	21891	CAAGAAAGGGUUGUGACA	2867
21891	GCUGUUUCUAAACCCAUGG	1217	21891	GCUGUUUCUAAACCCAUGG	1217	21909	CCAUGGGUUUAGAAACAGC	2868
21909	GGUACACAGACAUAUCUA	1218	21909	GGUACACAGACAUAUCUA	1218	21927	UAGUAUGUGUCUGUGUACC	2869
21927	AGUAUAUCGAUUAUGCAU	1219	21927	AGUAUAUCGAUUAUGCAU	1219	21945	UAGCAUUAUCGAUAUACAU	2870
21945	UUUAAUUGCACUUUCGAGU	1220	21945	UUUAAUUGCACUUUCGAGU	1220	21963	ACUCGAAAGUGCAAUUA	2871
21963	UACAUUAUCUGAUGCCUUUU	1221	21963	UACAUUAUCUGAUGCCUUUU	1221	21981	AAAAGGCAUCAGAUUAUGUA	2872
21981	UCGCUUGAUGUUUUCAGAAA	1222	21981	UCGCUUGAUGUUUUCAGAAA	1222	21999	UUUCUGAAACAUCAAGCGA	2873
21999	AAGUCAGGUAAUUUUAAAC	1223	21999	AAGUCAGGUAAUUUUAAAC	1223	22017	GUUUAAAAUUAACCGACUU	2874
22017	CACUUAACGAGUUUGUGU	1224	22017	CACUUAACGAGUUUGUGU	1224	22035	ACACAAACUCUCGUAAGUG	2875
22035	UUUAAAAUAAAGAUUGGGU	1225	22035	UUUAAAAUAAAGAUUGGGU	1225	22053	ACCCAUCUUUUUUUAAA	2876
22053	UUUCUCUAUGUUUUAAGG	1226	22053	UUUCUCUAUGUUUUAAGG	1226	22071	CCUUAUAAACUAUAGAAA	2877
22071	GGCUUAACCUUAUAGAU	1227	22071	GGCUUAACCUUAUAGAU	1227	22089	CACUUAUAGGUUAUAGGCC	2878
22089	GUAGUUCGUAUCUACCUU	1228	22089	GUAGUUCGUAUCUACCUU	1228	22107	AAGGUAGUACACGAACUAC	2879
22107	UCUGGUUUUAAACAUUUGA	1229	22107	UCUGGUUUUAAACAUUUGA	1229	22125	UCAAGUGUUAAAAACGAGA	2880
22125	AAACCUAUUUUUAAGUUGC	1230	22125	AAACCUAUUUUUAAGUUGC	1230	22143	GCAACUUAAAAAUAGGUUU	2881
22143	CCUCUUGGUUAUAAACAUUA	1231	22143	CCUCUUGGUUAUAAACAUUA	1231	22161	UAAUGUUAUUAACCAAGAGG	2882
22161	ACAAAUUUUAGAGCCAUC	1232	22161	ACAAAUUUUAGAGCCAUC	1232	22179	GAUUGGCUCUAAAAUUUGU	2883
22179	CUUACAGCCUUUUCACCUG	1233	22179	CUUACAGCCUUUUCACCUG	1233	22197	CAGGUGAAAAAGGUCUGUAG	2884
22197	GCUCAGACAUUUGGGGCA	1234	22197	GCUCAGACAUUUGGGGCA	1234	22215	UGCCCCAAUAGGUCUGAGC	2885
22215	ACGUCACGUCGAGCCUAUU	1235	22215	ACGUCACGUCGAGCCUAUU	1235	22233	AAUUGGUCGAGCUGUAGCGU	2886
22233	UUUGUUGGCUAUUUAAGC	1236	22233	UUUGUUGGCUAUUUAAGC	1236	22251	GCUUUAAAAUAGCCAACAAA	2887
22251	CCAACUAUUUAUUGCUCU	1237	22251	CCAACUAUUUAUUGCUCU	1237	22269	UGAGCAUAAAUUGUAGUUUG	2888
22269	AAGUAUGAUGAAAAUUGGUA	1238	22269	AAGUAUGAUGAAAAUUGGUA	1238	22287	UACCAUUUUCAUCAUACUU	2889
22287	ACAAUCACAGAUUGCUGUUG	1239	22287	ACAAUCACAGAUUGCUGUUG	1239	22305	CAACAGCAUCUGUGAUUUGU	2890
22305	GAUUGUUCUCAAUUCAC	1240	22305	GAUUGUUCUCAAUUCAC	1240	22323	GUGGAUUUUGAGAACAAUUC	2891
22323	CUUGCUGAACUCAAAUGCU	1241	22323	CUUGCUGAACUCAAAUGCU	1241	22341	AGCAUUUGAGUUUCAGCAAG	2892
22341	UCUGUUAAAGAGCUUUGAGA	1242	22341	UCUGUUAAAGAGCUUUGAGA	1242	22359	UCUCAAAAGCUCUUAACAGA	2893
22359	AUUGACAAGGAUUUUAACC	1243	22359	AUUGACAAGGAUUUUAACC	1243	22377	GGUAAAUUCCUUUGUCAAU	2894
22377	CAGACCUCUAAUUUCAGGG	1244	22377	CAGACCUCUAAUUUCAGGG	1244	22395	CCGUAAAAUUAAGAGGUCUG	2895
22395	GUUGUCCCCUAGGAGAU	1245	22395	GUUGUCCCCUAGGAGAU	1245	22413	CAUCUCCUGAGGGAACAC	2896
22413	GUUGUGAGAUUCCCUAAUA	1246	22413	GUUGUGAGAUUCCCUAAUA	1246	22431	UAUUAGGGAUUCUCACAAAC	2897
22431	AUUACAACUUUGUCCUU	1247	22431	AUUACAACUUUGUCCUU	1247	22449	AAGGACACAAGUUUUGUAAU	2898
22449	UUUGGAGAGGUUUUUAAG	1248	22449	UUUGGAGAGGUUUUUAAG	1248	22467	CAUUAAAAACCCUCUCCAAA	2899
22467	GCUACUAAAUUCCCUUCUG	1249	22467	GCUACUAAAUUCCCUUCUG	1249	22485	CAGAAGGGAAUUUAGUAGC	2900
22485	GUCUAUGCAUGGGGAGAGAA	1250	22485	GUCUAUGCAUGGGGAGAGAA	1250	22503	UUCUCUCCCAUUUUAUAGC	2901
22503	AAAAAAUUUCUAAUUGUG	1251	22503	AAAAAAUUUCUAAUUGUG	1251	22521	CACAUAUGAAAUUUUUUUU	2902
22521	GUUGCUUAUACUUGUGC	1252	22521	GUUGCUUAUACUUGUGC	1252	22539	GCACAGAGUAUUCAGCAAC	2903
22539	CUCUACAACUACAUIUU	1253	22539	CUCUACAACUACAUIUU	1253	22555	AAAAUUGUAGUUUGUAGAG	2904
22557	UUUUAACCCUUUAAGUGCU	1254	22557	UUUUAACCCUUUAAGUGCU	1254	22575	AGCACUUAAGGUUGAANA	2905

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22575	UAUGGCGUUUCUGCCACUA	1255	22575	UAUGGCGUUUCUGCCACUA	1255	22593	UAGUGGAGAAAACGCCAUA	2906
22593	AAGUUGAAGUACUUGCU	1256	22593	AAGUUGAAGUACUUGCU	1256	22611	AGCAAGAUCAUCAAU	2907
22611	UUCUCCAAUGUCUAGCAG	1257	22611	UUCUCCAAUGUCUAGCAG	1257	22629	CUGCAUAGACAUUGGAGAA	2908
22629	GAUUCUUUGUAGUCAAAG	1258	22629	GAUUCUUUGUAGUCAAAG	1258	22647	CCUUGACUACAAAAGAAUC	2909
22647	GGAGAUUUGUAGACAAA	1259	22647	GGAGAUUUGUAGACAAA	1259	22665	UUUGUCUUACAUCAUCC	2910
22665	AUAGCGCCAGGACAAACUG	1260	22665	AUAGCGCCAGGACAAACUG	1260	22683	CAGUUUGUCCUGGCGCUAU	2911
22683	GGUGUUAUUGCUGAUUAUA	1261	22683	GGUGUUAUUGCUGAUUAUA	1261	22701	UAUAUACAGCAUAACACC	2912
22701	AAUUAUAAUUGCCAGAUG	1262	22701	AAUUAUAAUUGCCAGAUG	1262	22719	CAUCUGGCAUUUAUUAUU	2913
22719	GAUUUAUGGUUGUGUCC	1263	22719	GAUUUAUGGUUGUGUCC	1263	22737	GGACAAACCCAUAGAAUC	2914
22737	CUUGCUUGGAUACUAGGA	1264	22737	CUUGCUUGGAUACUAGGA	1264	22755	UCCUAGUAUCCAAAGCAAG	2915
22755	AACAUUGAUGCUACUCAA	1265	22755	AACAUUGAUGCUACUCAA	1265	22773	UUGAAGUAGCAUAUUGUU	2916
22773	ACUGGUAAUUAUUAUUAUA	1266	22773	ACUGGUAAUUAUUAUUAUA	1266	22791	UAUAUUAUUAUUAUUAUUA	2917
22791	AAUAUAGGUACUUAUAGAC	1267	22791	AAUAUAGGUACUUAUAGAC	1267	22809	GUCUAAGAUACCUAUUAUU	2918
22809	CAUGGCAAGCUUAGGCCCU	1268	22809	CAUGGCAAGCUUAGGCCCU	1268	22827	AGGGCCUAAGCUUAGGCCAUG	2919
22827	UUUGAGAGAGACAUUAUCUA	1269	22827	UUUGAGAGAGACAUUAUCUA	1269	22845	UAGUAUUGUCUCUCUCAAA	2920
22845	AAUGUGCCUUUCUCCUG	1270	22845	AAUGUGCCUUUCUCCUG	1270	22863	CAGGGGAGAAAGGCACAUU	2921
22863	GAUGGCAAAACCUUGCACCC	1271	22863	GAUGGCAAAACCUUGCACCC	1271	22881	GGUGCAAGGUUUGGCAUC	2922
22881	CCACUGCUCUUAUUGUU	1272	22881	CCACUGCUCUUAUUGUU	1272	22899	AACAAUUAAGAGCAGGUGG	2923
22899	UAUUGGCCAUUAUUAUUAU	1273	22899	UAUUGGCCAUUAUUAUUAU	1273	22917	AAUCAUUUAUUGGCCAAUA	2924
22917	UAUGGUUUUAACACCACUA	1274	22917	UAUGGUUUUAACACCACUA	1274	22935	UAGUGGUGUAAUAAACCAUA	2925
22935	ACUGGCAUUGGUUACCAAC	1275	22935	ACUGGCAUUGGUUACCAAC	1275	22953	GUUGUAGCCAAUUGGCCAGU	2926
22953	CCUUAACAGUUGUAGUAC	1276	22953	CCUUAACAGUUGUAGUAC	1276	22971	GUUAACAACUCUGUAAGG	2927
22971	CUUUCUUUUGAACUUAUA	1277	22971	CUUUCUUUUGAACUUAUA	1277	22989	UUAUAAUUAUCAAAGAAAG	2928
22989	AAUGCACCAGCCACCGUUU	1278	22989	AAUGCACCAGCCACCGUUU	1278	23007	AAACCGUGGCGGUGCAUU	2929
23007	UGUGACCAAAUUAUCCA	1279	23007	UGUGACCAAAUUAUCCA	1279	23025	UGGAUAAUUUUGGUCCACA	2930
23025	ACUGACCUUAUUAAGAAC	1280	23025	ACUGACCUUAUUAAGAAC	1280	23043	GGUUCUUUAUUAAGGUCAGU	2931
23043	CAGUGUACAUAUUAUUAU	1281	23043	CAGUGUACAUAUUAUUAU	1281	23061	AAUUAUUAUUAAGACACACUG	2932
23061	UUUAUUGGACUCACUGGUA	1282	23061	UUUAUUGGACUCACUGGUA	1282	23079	UACCAGUGAGUCCAUUAAA	2933
23079	ACUGGUGUUAUUAUCCUU	1283	23079	ACUGGUGUUAUUAUCCUU	1283	23097	AAGGAGUUUAACACACCAGU	2934
23097	UCUCAAAGAGAUUAUCAA	1284	23097	UCUCAAAGAGAUUAUCAA	1284	23115	GUUAAAUCUCUUUUGAAGA	2935
23115	CCAUUUAACAUAUUGGCC	1285	23115	CCAUUUAACAUAUUGGCC	1285	23133	GGCCAAUUGUUGAAUUGG	2936
23133	CGUGAUUUUCUGAUUUAUA	1286	23133	CGUGAUUUUCUGAUUUAUA	1286	23151	UGAAUACAGAAACAACAG	2937
23151	ACUGAUUCCGUUCGAGAU	1287	23151	ACUGAUUCCGUUCGAGAU	1287	23169	GAUCUCGAACGGAUACAGU	2938
23169	CCUAAAACAUUCUGAAUUAU	1288	23169	CCUAAAACAUUCUGAAUUAU	1288	23187	AUAUUUACAGAUUUUUUAGG	2939
23187	UUAAGAUUUUACCUUGCG	1289	23187	UUAAGAUUUUACCUUGCG	1289	23205	CGCAAGGUGAAUUGUCUAA	2940
23205	GCUUUUGGGGUGUAAGUG	1290	23205	GCUUUUGGGGUGUAAGUG	1290	23223	CACUUAACCCCCCAAAAGC	2941
23223	GUAAUUAACCCUGGAACAA	1291	23223	GUAAUUAACCCUGGAACAA	1291	23241	UUUUUCCAGGUGUAUUUAC	2942
23241	AUUGCUUAUCUGAAGUUG	1292	23241	AUUGCUUAUCUGAAGUUG	1292	23259	CAACUUCAGAUUAAGCAUU	2943
23259	GCUGUUCUAUAUCAAAGU	1293	23259	GCUGUUCUAUAUCAAAGU	1293	23277	CAUCUUGAUUAUUAAGCAGC	2944
23277	GUUAACUGCACUGAUUUU	1294	23277	GUUAACUGCACUGAUUUU	1294	23295	AAACAUCAGUGCAGUUAAC	2945
23295	UCUACAGCAUUAUUGCAG	1295	23295	UCUACAGCAUUAUUGCAG	1295	23313	CUGCAUGAAUUGCUGUAGA	2946
23313	GAUCAACUCACACACGCUU	1296	23313	GAUCAACUCACACACGCUU	1296	23331	AAGCUGGUGUGAGUUGAUC	2947

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23331	UGGCGCAUAUAUUCUACUG	1297	23331	UGGCGCAUAUAUUCUACUG	1297	23349	CAGUAGAAUAUAUUGCGCCA	2948
23349	GGAAACAAUGAUUCCAGA	1298	23349	GGAAACAAUGAUUCCAGA	1298	23367	UCUGGAUAUAUUGUUC	2949
23367	ACUAAGCAGGCGUCUUA	1299	23367	ACUAAGCAGGCGUCUUA	1299	23385	UAAGACAGCCUGCUAGAU	2950
23385	AUAGGAGCUGAGCAUGCG	1300	23385	AUAGGAGCUGAGCAUGCG	1300	23403	CGACAUUCAGCUCUUAU	2951
23403	GACAUUCUUAUGAGGCG	1301	23403	GACAUUCUUAUGAGGCG	1301	23421	CGCACUCAAAAGAGUGUC	2952
23421	GACAUUCUUAUGAGGCG	1302	23421	GACAUUCUUAUGAGGCG	1302	23439	CAGCUCCAAUAGGAAUGUC	2953
23439	GGCAUUGUGCUAGUUAAC	1303	23439	GGCAUUGUGCUAGUUAAC	1303	23457	GGUAACUAGCACAAUUGCC	2954
23457	CAUACAGUUCUUAUUAAC	1304	23457	CAUACAGUUCUUAUUAAC	1304	23475	GUAAUAAAGAAACUGUAUG	2955
23475	CGUAGUACUAGCCAAAUAU	1305	23475	CGUAGUACUAGCCAAAUAU	1305	23493	AUUUUGGCUAGUACUAGC	2956
23493	UCUAUUGUGGCUUAUUAUA	1306	23493	UCUAUUGUGGCUUAUUAUA	1306	23511	UAGUAUAAGCCACAAUAGA	2957
23511	AUGUCUUAAGGUGCGUAUA	1307	23511	AUGUCUUAAGGUGCGUAUA	1307	23529	UAUCAGCACCUAAGACAU	2958
23529	AGUUCAAUUGCUUACUCUA	1308	23529	AGUUCAAUUGCUUACUCUA	1308	23547	UAGAGUAAGCAAUUGAACU	2959
23547	AAUAAACCAUUGCUUAUAC	1309	23547	AAUAAACCAUUGCUUAUAC	1309	23565	GUAAAGCAAUGGUGUUAU	2960
23565	CCUACUAACUUUCAAUAUA	1310	23565	CCUACUAACUUUCAAUAUA	1310	23583	UAUUGAAAAUUAUAGG	2961
23583	AGUAUUAACUACAGAAUAUA	1311	23583	AGUAUUAACUACAGAAUAUA	1311	23601	UUACUUCUGUAGUAAUGCU	2962
23601	AUGCCUGUUCUUAUGGCUA	1312	23601	AUGCCUGUUCUUAUGGCUA	1312	23619	UAGCCAUAGAAACAGGCAU	2963
23619	AAACCCUCCGUAUAUUAUA	1313	23619	AAACCCUCCGUAUAUUAUA	1313	23637	UACAAUCUACGGAGGUUUU	2964
23637	AAUAUGUACUUCGCGGAG	1314	23637	AAUAUGUACUUCGCGGAG	1314	23655	CUCCGCAGUAGUACAUAU	2965
23655	GAUUCUACUAGAAUGGCUA	1315	23655	GAUUCUACUAGAAUGGCUA	1315	23673	UAGCACAUUCAGUAGAAUC	2966
23673	AAUUGCUUCUCCAAUAUG	1316	23673	AAUUGCUUCUCCAAUAUG	1316	23691	CAUAUUGGAGAAACAAUUA	2967
23691	GGUAGCUUUUGCACACAAC	1317	23691	GGUAGCUUUUGCACACAAC	1317	23709	GUUGUGUGCAAAAGCUACC	2968
23709	CUAAUUGGUCACUCUCAG	1318	23709	CUAAUUGGUCACUCUCAG	1318	23727	CUGAGAGCAGCAGCAUUAU	2969
23727	GGUAUUGGUCUGAACAGG	1319	23727	GGUAUUGGUCUGAACAGG	1319	23745	CCUGUUCAGCAGCAUAUCC	2970
23745	GAUGCAACACACGUGAAG	1320	23745	GAUGCAACACACGUGAAG	1320	23763	CUACAGUGUGUUGCGAUC	2971
23763	GUGUUCGCUCAAGUCAAAC	1321	23763	GUGUUCGCUCAAGUCAAAC	1321	23781	GUUUGACUUGAGCGAACAC	2972
23781	CAAAUGUACAAACCCCAA	1322	23781	CAAAUGUACAAACCCCAA	1322	23799	UUGGGUUUUGUACAUAUUG	2973
23799	ACUUUGAAUAUUUUGGUG	1323	23799	ACUUUGAAUAUUUUGGUG	1323	23817	CACCAAAUAUUUCAAAGU	2974
23817	GGUUUUAUUUUUACAAA	1324	23817	GGUUUUAUUUUUACAAA	1324	23835	UUUGUGAAAAUUUAAAACC	2975
23835	AUAUACCGACCCUCUAA	1325	23835	AUAUACCGACCCUCUAA	1325	23853	UAGAGGGUCAGGUAAUAU	2976
23853	AAGCCAAUAAGAGGUCUU	1326	23853	AAGCCAAUAAGAGGUCUU	1326	23871	AAGACCUUUAUUGGCUU	2977
23871	UUUAUUGAGGACUUGCUCU	1327	23871	UUUAUUGAGGACUUGCUCU	1327	23889	AGAGCAAGUCCUCAAUAA	2978
23889	UUUAUUAAGGUGACACUCG	1328	23889	UUUAUUAAGGUGACACUCG	1328	23907	CGAGUGUCACCUUAUAAA	2979
23907	GCUGAUGCUGGCUUCAUGA	1329	23907	GCUGAUGCUGGCUUCAUGA	1329	23925	UCAUGAAGCCAGCAUCAGC	2980
23925	AAGCAAUAUGGCGAAUGCC	1330	23925	AAGCAAUAUGGCGAAUGCC	1330	23943	GGCAUUGCCAUUAUUGCUU	2981
23943	CUAGGUGAUUAUUAUUAUA	1331	23943	CUAGGUGAUUAUUAUUAUA	1331	23961	UAGCAUUAUAUACCUUAG	2982
23961	AGAGAUUCUUAUUGGCGC	1332	23961	AGAGAUUCUUAUUGGCGC	1332	23979	GCGCACAAUAGAGAUUCU	2983
23979	CAGAAUUAUUAUUGGACUUA	1333	23979	CAGAAUUAUUAUUGGACUUA	1333	23997	UAAGUCCAUUAGAAUUCUG	2984
23997	ACAGUGUUGCCACCCUCUG	1334	23997	ACAGUGUUGCCACCCUCUG	1334	24015	GCAGAGGUGGCAACACUGU	2985
24015	CUCACUGAUGAUUAUUAU	1335	24015	CUCACUGAUGAUUAUUAU	1335	24033	CAUAUUAUUAUACAGUGAG	2986
24033	GCUGCCUACUAGCUGCUC	1336	24033	GCUGCCUACUAGCUGCUC	1336	24051	GAGCAGCAGUAGGCGAGC	2987
24051	CUAGUUAUGGUGUACGCCA	1337	24051	CUAGUUAUGGUGUACGCCA	1337	24069	UGGCAUACCCACUAAUAG	2988
24069	ACUGCUGGAGGACAUUUG	1338	24069	ACUGCUGGAGGACAUUUG	1338	24087	CAAAUGUCCAUCCAGCAGU	2989

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24087	GGUGUGGCGUGCUCUUC	1339	24087	GGUGUGGCGUGCUCUUC	1339	24105	GAAGAGCAGCGCCAGCACC	2990
24105	CAAAUACCUUUUUGCUAUGC	1340	24105	CAAAUACCUUUUUGCUAUGC	1340	24123	GCAUAGCAAAAAGGUUUUG	2991
24123	CAAAUGGCAUAUAGGUUA	1341	24123	CAAAUGGCAUAUAGGUUA	1341	24141	UGAACCUUAUAGCCAUUUG	2992
24141	AAUGGCAUUGGAGUUAUCC	1342	24141	AAUGGCAUUGGAGUUAUCC	1342	24159	GGUAAACUCCAAUUGCCAUU	2993
24159	CAAAUUGUUCUCUAUGAGA	1343	24159	CAAAUUGUUCUCUAUGAGA	1343	24177	UCUCAUAGAGAACAUUUUG	2994
24177	AACCAAAACAAUUCGCCA	1344	24177	AACCAAAACAAUUCGCCA	1344	24195	UGCGAUUUUGUUUUUGGUU	2995
24195	AACCAUUUAACAAGGCCA	1345	24195	AACCAUUUAACAAGGCCA	1345	24213	UCGCCUUUGUAAAUUGGUU	2996
24213	AUUAGUCAAUUUAAGAAU	1346	24213	AUUAGUCAAUUUAAGAAU	1346	24231	AUUUUUGAAUUUGACUAAU	2997
24231	UCACUUAACAACAACUAA	1347	24231	UCACUUAACAACAACUAA	1347	24249	UUGAUUUUGUUAAGUGA	2998
24249	ACUGCAUUGGCAAGCUGC	1348	24249	ACUGCAUUGGCAAGCUGC	1348	24267	GCAGCUUGGCCAAUUGCAGU	2999
24267	CAAGACGUUUUAACCGA	1349	24267	CAAGACGUUUUAACCGA	1349	24285	UCUGUUUAACAACGUCUUG	3000
24285	AUGCUCUAGCAUUAACA	1350	24285	AUGCUCUAGCAUUAACA	1350	24303	UGUUUAUUCUUGAGCAU	3001
24303	ACACUUGUUAACAACUUA	1351	24303	ACACUUGUUAACAACUUA	1351	24321	UAAGUUUGUUUAACAAGUGU	3002
24321	AGCUCUAUUUUGGUGCAA	1352	24321	AGCUCUAUUUUGGUGCAA	1352	24339	UUGCACCAAAAUUJAGAGCU	3003
24339	AUUUCAAGUGUGCUAAUUG	1353	24339	AUUUCAAGUGUGCUAAUUG	1353	24357	CAUUUAGCACACUUGAAU	3004
24357	GAUACCUUUUGCGACUUG	1354	24357	GAUACCUUUUGCGACUUG	1354	24375	CAAGUCGGGAAAGGAUAC	3005
24375	GAUAAUGCGAGCGGAGG	1355	24375	GAUAAUGCGAGCGGAGG	1355	24393	CCUCCGCCUCGACUUUAUC	3006
24393	GUACAAUUGACAGGUUA	1356	24393	GUACAAUUGACAGGUUA	1356	24411	UUAACCGUCACAUUUUJAC	3007
24411	AUUACAGGCAGACUUCAAA	1357	24411	AUUACAGGCAGACUUCAAA	1357	24429	UUUAGAGUCGCGCUUUAU	3008
24429	AGCCUCAAACCUUAUGUA	1358	24429	AGCCUCAAACCUUAUGUA	1358	24447	UUUAUAGGUUUUGAGGCU	3009
24447	ACACUUAACUUAACAGG	1359	24447	ACACUUAACUUAACAGG	1359	24465	CCUUGAUUUAUUGUUGUGU	3010
24465	CGUCGUAUAUACAGGCUU	1360	24465	CGUCGUAUAUACAGGCUU	1360	24483	AAGCCUGAUUUUCAGCAGC	3011
24483	UCUGCUAAUUCUUGCUCUA	1361	24483	UCUGCUAAUUCUUGCUCUA	1361	24501	UAGCAGAAAGAUUJAGCAGA	3012
24501	ACUAAAUGUCUGAGUGUG	1362	24501	ACUAAAUGUCUGAGUGUG	1362	24519	CACACUCAGACAUUUJAGU	3013
24519	GUUCUUGGACAAUCAAUA	1363	24519	GUUCUUGGACAAUCAAUA	1363	24537	UUUUUGAUUUGUCCAAAGAC	3014
24537	AGAUUGACUUUUGUGGAA	1364	24537	AGAUUGACUUUUGUGGAA	1364	24555	UUCACAAAAGUCAAACUCU	3015
24555	AAGGGCUAACCCCUUAUGU	1365	24555	AAGGGCUAACCCCUUAUGU	1365	24573	ACAUAAAGGUGUAGCCCUU	3016
24573	UCCUCCCAACAAGCAGCCC	1366	24573	UCCUCCCAACAAGCAGCCC	1366	24591	GGCUGCUUUGUGGGAAGGA	3017
24591	CCGCAUGGUGUUGUCUUC	1367	24591	CCGCAUGGUGUUGUCUUC	1367	24609	GGAAGACAAACACCAUGCGG	3018
24609	CUACAUGUCACGUUUGUC	1368	24609	CUACAUGUCACGUUUGUC	1368	24627	GCACAUACGUGACAUUGAG	3019
24627	CCAUCCAGGAGAGGAACU	1369	24627	CCAUCCAGGAGAGGAACU	1369	24645	AGUCCUCUCCUGGGAUGG	3020
24645	UUCACACAGCGCCAGCAA	1370	24645	UUCACACAGCGCCAGCAA	1370	24663	UUGCUGGCGCUGUGGUGAA	3021
24663	AUUUGUCAUGAAGGCAAAG	1371	24663	AUUUGUCAUGAAGGCAAAG	1371	24681	CUUUGCCUUAUGACACAAU	3022
24681	GCAUACUCCUCCUGGAGAG	1372	24681	GCAUACUCCUCCUGGAGAG	1372	24699	CUUCACGAGGGAAGUAUGC	3023
24699	GGUGUUUUUGUUAUUAUG	1373	24699	GGUGUUUUUGUUAUUAUG	1373	24717	CAUUAACACAAAACACACC	3024
24717	GGACAUUCUUGGUUAUUA	1374	24717	GGACAUUCUUGGUUAUUA	1374	24735	UAAUAAACCAAGGAAGGCC	3025
24735	ACACAGAGAAUUCUUAU	1375	24735	ACACAGAGAAUUCUUAU	1375	24753	AAAAGAUUCCUCUGUGU	3026
24753	UCUCCACAAAUUAUUAUA	1376	24753	UCUCCACAAAUUAUUAUA	1376	24771	UAGUAAUUAUUUGUGGAGA	3027
24771	ACAGACAAUUAUUAUUGU	1377	24771	ACAGACAAUUAUUAUUGU	1377	24789	AGACAAUUAUUAUUGUCUGU	3028
24789	UCAGGAAUUAUUGAUGUG	1378	24789	UCAGGAAUUAUUGAUGUG	1378	24807	CGACAUACAUAUUAUCCUGA	3029
24807	GUUAUUGGCAUUAUUAACA	1379	24807	GUUAUUGGCAUUAUUAACA	1379	24825	UGUUAUUAUUAUUAUUAAC	3030
24825	AACACAGUUUAUUAUUAU	1380	24825	AACACAGUUUAUUAUUAU	1380	24843	GAGGAUUAUUAUUAUUAU	3031

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24843	CUGCAACCUUGAGCUUGACU	1381	24843	CUGCAACCUUGAGCUUGACU	1381	24861	AGUCAAGCUCAGGUUGCAG	3032
24861	UCAUUCAAAAGAGAGCUGG	1382	24861	UCAUUCAAAAGAGAGCUGG	1382	24879	CCAGCUCUUCUUUGAUGA	3033
24879	GACAAGUACUUCAAAACUC	1383	24879	GACAAGUACUUCAAAACUC	1383	24897	GAUUUUUGAAGUACUUGUC	3034
24897	CAUACAUCACCCAGAUUG	1384	24897	CAUACAUCACCCAGAUUG	1384	24915	CAACAUCUGGUGAUGUAUG	3035
24915	GAUCUUUGGCACAUUCAG	1385	24915	GAUCUUUGGCACAUUCAG	1385	24933	CUGAAAUGUGCCCAAGC	3036
24933	GGCAUUAACGCUUCUGCG	1386	24933	GGCAUUAACGCUUCUGCG	1386	24951	CGAAGAAGCGUUAAUGCC	3037
24951	GUCAACAUCAAAAGAAA	1387	24951	GUCAACAUCAAAAGAAA	1387	24969	UUUUAUUUGAAUUGUAGC	3038
24969	AUUGACCGCCUCAAUGAGG	1388	24969	AUUGACCGCCUCAAUGAGG	1388	24987	CCUCAUUGAGCGGCUCAAU	3039
24987	GUCGUAUUUUUUAAUG	1389	24987	GUCGUAUUUUUUAAUG	1389	25005	CAUUUAAUUUUUAGCGAC	3040
25005	GAUACACUUAUGACCUUC	1390	25005	GAUACACUUAUGACCUUC	1390	25023	GAAGGCUAAUGAGUUAUC	3041
25023	CAAGAAUUGGAAAUAUG	1391	25023	CAAGAAUUGGAAAUAUG	1391	25041	CAUAUUUCCCAAUUCUUG	3042
25041	GAGCAUAUAUAAUUGGC	1392	25041	GAGCAUAUAUAAUUGGC	1392	25059	GCCAUIUAUAUUAUUGCUC	3043
25059	CCUUGGUAUGUUUGGCUCG	1393	25059	CCUUGGUAUGUUUGGCUCG	1393	25077	CGAGCCAAACAUACCAAGG	3044
25077	GGCUCAUUGGAGCUAA	1394	25077	GGCUCAUUGGAGCUAA	1394	25095	UUAUCCAGCAUUGAAGCC	3045
25095	AUUGCCAUUGCUAGGUUA	1395	25095	AUUGCCAUUGCUAGGUUA	1395	25113	UAACCAUAGCGAUGGCAU	3046
25113	ACAAUCUUGCUUUGUUGCA	1396	25113	ACAAUCUUGCUUUGUUGCA	1396	25131	UGCAACAAGCAAGAUUGU	3047
25131	AUGACUAGUUGUUGCAGUU	1397	25131	AUGACUAGUUGUUGCAGUU	1397	25149	AACUGCAACAUAGUCAU	3048
25149	UGCCUCAAGGUGCAUGCU	1398	25149	UGCCUCAAGGUGCAUGCU	1398	25167	AGCAUGACCCUUGAGGCA	3049
25167	UCUUGUGGUUCUUGCUGCA	1399	25167	UCUUGUGGUUCUUGCUGCA	1399	25185	UGCAGCAAGAACCAAGA	3050
25185	AAGUUUGAGGAGGAGUACU	1400	25185	AAGUUUGAGGAGGAGUACU	1400	25203	AGUCAUCCUACAACAAU	3051
25203	UCUGAGCCAGUUCUCAAGG	1401	25203	UCUGAGCCAGUUCUCAAGG	1401	25221	CCUUGAGAUCUGGUCAGA	3052
25221	GGUGUCAAUUUACAUA	1402	25221	GGUGUCAAUUUACAUA	1402	25239	UGUAUUAUUUUGACACC	3053
25239	ACUAUAAAGCAUUAUGGA	1403	25239	ACUAUAAAGCAUUAUGGA	1403	25257	UCCAUAAGUUGUUAUUGU	3054
25257	AUUUGUUUAUGAGAUUUU	1404	25257	AUUUGUUUAUGAGAUUUU	1404	25275	AAAAUUCUAUAAACAAU	3055
25275	UAACUCUUGGAUCAAUAC	1405	25275	UAACUCUUGGAUCAAUAC	1405	25293	GUAAUUGAUCCAAGAGUAA	3056
25293	CUGCACAGCCAGUAAAAU	1406	25293	CUGCACAGCCAGUAAAAU	1406	25311	AUUUUACUGGCUUGCAG	3057
25311	UUGACAAUGCUUCUCCUGC	1407	25311	UUGACAAUGCUUCUCCUGC	1407	25329	GCAGGAGAAGCAUUGUCAA	3058
25329	CAAGUACUUAUGCUAC	1408	25329	CAAGUACUUAUGCUAC	1408	25347	GUAGCAUGAACAGUACUUG	3059
25347	CAGCAACGAUACCGCUACA	1409	25347	CAGCAACGAUACCGCUACA	1409	25365	UGUAGCGUAUCGUUGCUG	3060
25365	AAGCCUCACUCCUUUCGG	1410	25365	AAGCCUCACUCCUUUCGG	1410	25383	CCGAAAAGGAGUGAGGCUU	3061
25383	GAUGGCUUUAUUGGCGU	1411	25383	GAUGGCUUUAUUGGCGU	1411	25401	ACGCCAAUAAACAGCCAU	3062
25401	UUGCAUUUCUUGCUGUUU	1412	25401	UUGCAUUUCUUGCUGUUU	1412	25419	AAACAGCAAGAAUUGCAA	3063
25419	UUCAGAGCGCUACCAAAU	1413	25419	UUCAGAGCGCUACCAAAU	1413	25437	AUUUUGGUAUCGCUUGAA	3064
25437	UAAUUGCGCUCAUAAAAA	1414	25437	UAAUUGCGCUCAUAAAAA	1414	25455	CUUUUAUUGAGCGCAUUA	3065
25455	GAUGGACGUAAGCCUUUA	1415	25455	GAUGGACGUAAGCCUUUA	1415	25473	UAAAGGCUAGCUGGCCAU	3066
25473	AUAAGGCUUCCAGUUAU	1416	25473	AUAAGGCUUCCAGUUAU	1416	25491	AUGAACUGGAAGCCCUUAU	3067
25491	UUUGCAUUUACUGCUGCU	1417	25491	UUUGCAUUUACUGCUGCU	1417	25509	AGCAGCAGUAAAUUGCAAA	3068
25509	UAUUUGUUAACCAUUAUC	1418	25509	UAUUUGUUAACCAUUAUC	1418	25527	GAUAAGAGGUAAACAAUA	3069
25527	CACAUCUUUUGCUGCGC	1419	25527	CACAUCUUUUGCUGCGC	1419	25545	CGGACAAGCAAAAGUUG	3070
25545	CUGCAGGUUAGGAGCGCA	1420	25545	CUGCAGGUUAGGAGCGCA	1420	25563	UGCGCCUCCAUACUGCAG	3071
25563	AAUUUUUGUACCUUAUGC	1421	25563	AAUUUUUGUACCUUAUGC	1421	25581	GCAUAGAGGUACAAAUU	3072
25581	CCUUGAUUAUUUUUCUACA	1422	25581	CCUUGAUUAUUUUUCUACA	1422	25599	UGUAGAAAAUAUUAUCAAGG	3073

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25599	AAUGCAUACGCAUGAG	1423	25599	AAUGCAUACGCAUGAG	1423	25617	CUACAUGCUUGAUGCAUU	3074
25617	GAUUUAUUAUGAUGUUG	1424	25617	GAUUUAUUAUGAUGUUG	1424	25635	CAACAUCUGUAUUAUUUC	3075
25635	GGCUUUGUUGGAAGUGCAA	1425	25635	GGCUUUGUUGGAAGUGCAA	1425	25653	UUGCACUUCACAAAGGCC	3076
25653	AAUCCAAGAACCCAUUACU	1426	25653	AAUCCAAGAACCCAUUACU	1426	25671	AGUAUUGGUUUCUUGGAUU	3077
25671	UUUAUGAUGCCAAUACUU	1427	25671	UUUAUGAUGCCAAUACUU	1427	25689	AAGUAGUUGGCAUCAAUA	3078
25689	UUUUUGGUGGCAACACACA	1428	25689	UUUUUGGUGGCAACACACA	1428	25707	UGUGUGCCAGCAAAACA	3079
25707	AUAACUAGACUACUGUUAU	1429	25707	AUAACUAGACUACUGUUAU	1429	25725	AUACAGUAGUAGUUAUU	3080
25725	UACCAUAUAACAGUGUCAC	1430	25725	UACCAUAUAACAGUGUCAC	1430	25743	GUGACACUAGUUAUUGGUA	3081
25743	CAGUAACAAUUGUCGUUAC	1431	25743	CAGUAACAAUUGUCGUUAC	1431	25761	GUACGACAAUUGUACUG	3082
25761	CUGAAGGUGACGGCAUUUC	1432	25761	CUGAAGGUGACGGCAUUUC	1432	25779	GAUUGCCGUCACCUUCAG	3083
25779	CAACACCAAAACUCAAAGA	1433	25779	CAACACCAAAACUCAAAGA	1433	25797	UCUUUGAGUUUUGGUGUUG	3084
25797	AAGACUACCAAAUUGGUGG	1434	25797	AAGACUACCAAAUUGGUGG	1434	25815	CCUACAAUUGGUGUUCUU	3085
25815	GUUAUUCUGAGGAUAGGCA	1435	25815	GUUAUUCUGAGGAUAGGCA	1435	25833	UGCCUAUCCUCAGAAUAC	3086
25833	ACUCAGGUGUUAAGACUA	1436	25833	ACUCAGGUGUUAAGACUA	1436	25851	UAGUCUUUAACACCCUGAGU	3087
25851	AUGUCGUUGUACAUUGGCUA	1437	25851	AUGUCGUUGUACAUUGGCUA	1437	25869	UAGCCAUUGUACACGACAU	3088
25869	AUUUCACCGAAGUUUACUA	1438	25869	AUUUCACCGAAGUUUACUA	1438	25887	UAGUAAACUUCGGUGAAAU	3089
25887	ACCAGCUUGAGUCUACACA	1439	25887	ACCAGCUUGAGUCUACACA	1439	25905	UGUGUAGACUCAGGUGGU	3090
25905	AAAUUACUACAGACACUGU	1440	25905	AAAUUACUACAGACACUGU	1440	25923	CCAGUUGCUGUAGUAAUUU	3091
25923	GUUAUGAAAUUGCUACAUAU	1441	25923	GUUAUGAAAUUGCUACAUAU	1441	25941	AUUGUAGCUUUUUAUUAUAC	3092
25941	UCUUAUUAUUAACAGCU	1442	25941	UCUUAUUAUUAACAGCU	1442	25959	AGCUUUGUUAAGUAGAA	3093
25959	UUGUUAAGACCCACCGAA	1443	25959	UUGUUAAGACCCACCGAA	1443	25977	UUCGGUGGUCUUAUACAA	3094
25977	AUGUGAAAUACACACAAU	1444	25977	AUGUGAAAUACACACAAU	1444	25995	AUUGUGUUAUUUGGACAU	3095
25995	UCGACGGUCUUCAGGAGU	1445	25995	UCGACGGUCUUCAGGAGU	1445	26013	ACUCCUGAAGCCGUGCGA	3096
26013	UUGCUAAUCCAGCAUUGGA	1446	26013	UUGCUAAUCCAGCAUUGGA	1446	26031	UCCAUIUGUGUUAUAGCAA	3097
26031	AUCCAUIUUAUGAUGGCC	1447	26031	AUCCAUIUUAUGAUGGCC	1447	26049	GGCUAUCUAAAUUUGGAU	3098
26049	CGACGACGACUACUAGCGU	1448	26049	CGACGACGACUACUAGCGU	1448	26067	ACGCUAGUAGUCGUGUGC	3099
26067	UGCCUUUGUAAGCACAAGA	1449	26067	UGCCUUUGUAAGCACAAGA	1449	26085	UCUUGGCUUACAAAGGCA	3100
26085	AAAGUGAGUACGAACUUAU	1450	26085	AAAGUGAGUACGAACUUAU	1450	26103	AUAAGUUGUACUACUUAU	3101
26103	UGUACUUAUUGUUAUUGGA	1451	26103	UGUACUUAUUGUUAUUGGA	1451	26121	UCCGAAACGAAUAGAGUACA	3102
26121	AAGAAACAGGUACGUUAU	1452	26121	AAGAAACAGGUACGUUAU	1452	26139	AUUAACGUACCGUUAUUCU	3103
26139	UAGUUAUUAAGCGUACUUCU	1453	26139	UAGUUAUUAAGCGUACUUCU	1453	26157	AGAAGUACCGUUAUUAACUA	3104
26157	UUUUUCUUGCUUUCGUGGU	1454	26157	UUUUUCUUGCUUUCGUGGU	1454	26175	ACCACGAAAGCAAGAAAA	3105
26175	UAUUCUUGCUAGUCACACU	1455	26175	UAUUCUUGCUAGUCACACU	1455	26193	AGUGGACUAGCAAGAAUA	3106
26193	UAGCAUCCUUAUCUGCGCU	1456	26193	UAGCAUCCUUAUCUGCGCU	1456	26211	AGCGCAGUAGGAGUGGCUA	3107
26211	UUCGAUUGUGGCGUACUG	1457	26211	UUCGAUUGUGGCGUACUG	1457	26229	CAGUACGACACAAUUCGAA	3108
26229	GCUGCAUAUUGUUAACGU	1458	26229	GCUGCAUAUUGUUAACGU	1458	26247	ACGUUAACAAUUAUUGCAGC	3109
26247	UGAGUUUAUUAACCAAC	1459	26247	UGAGUUUAUUAACCAAC	1459	26265	GUUGUUUAUUAUUAACUUA	3110
26265	CGGUUAACGUCUACUCGCG	1460	26265	CGGUUAACGUCUACUCGCG	1460	26283	CGCGAGUAGACGUAAACCG	3111
26283	GUGUUAUUAUUAUUAUUAU	1461	26283	GUGUUAUUAUUAUUAUUAU	1461	26301	GAGUUCAGAUUUUAACAC	3112
26301	CUUCUGAAGGAGUUCUGA	1462	26301	CUUCUGAAGGAGUUCUGA	1462	26319	UCAGGAACUCCUUCAGAA	3113
26319	AUCUUCUGGUCUUAACGAA	1463	26319	AUCUUCUGGUCUUAACGAA	1463	26337	UUCGUUAAGACCAAGAAU	3114
26337	ACUACUAUUAUUAUUAU	1464	26337	ACUACUAUUAUUAUUAU	1464	26355	AUAUAUUAUUAUUAUUAU	3115

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26355	UCUGUUUGGAACUUUAACA	1465	26355	UCUGUUUGGAACUUUAACA	1465	26373	UGUUAAAGUUCACAAACAGA	3116
26373	AUUGCUUAUUAUGGCAGAC	1466	26373	AUUGCUUAUUAUGGCAGAC	1466	26391	GUCUGCCAUGAAAGCAAU	3117
26391	CAACGGUACUUAUACCGUU	1467	26391	CAACGGUACUUAUACCGUU	1467	26409	AACGGUAAUAGUACCGUUG	3118
26409	UGAGGAGCUUAACAACUC	1468	26409	UGAGGAGCUUAACAACUC	1468	26427	GAGUUGUUAAAGCUCCUCA	3119
26427	CCUGGAACAAUGGAACCUA	1469	26427	CCUGGAACAAUGGAACCUA	1469	26445	UAGGUCCAUUUGUCCAGG	3120
26445	AGUAAUAGGUUCCUAUUC	1470	26445	AGUAAUAGGUUCCUAUUC	1470	26463	GAUAGGAAACCUAUUACU	3121
26463	CCUAGCCUGGAUUAUUA	1471	26463	CCUAGCCUGGAUUAUUA	1471	26481	UAACAUAUCCAGGCUUAGG	3122
26481	ACUACAAUUGCCUAUUCU	1472	26481	ACUACAAUUGCCUAUUCU	1472	26499	AGAAUAGGCAAAUUGUAGU	3123
26499	UAUCCGGAACAGGUUUUG	1473	26499	UAUCCGGAACAGGUUUUG	1473	26517	CAAAAACCUUUCGCGAUUA	3124
26517	GUACAAUAAAGCUUUGU	1474	26517	GUACAAUAAAGCUUUGU	1474	26535	AACAAGCUUUAUUAUGUAC	3125
26535	UUUCCUCUGGCUCUUGUGG	1475	26535	UUUCCUCUGGCUCUUGUGG	1475	26553	CCACAAGAGCCAGAGGAAA	3126
26553	GCCAGUAAACUUGCUUGU	1476	26553	GCCAGUAAACUUGCUUGU	1476	26571	ACAAGCAAGUUAUCUGGC	3127
26571	UUUUGUCUUGCUGCUGUC	1477	26571	UUUUGUCUUGCUGCUGUC	1477	26589	GACAGCAGCAAGCACAAA	3128
26589	CUACAGAAUAAUUGGGUG	1478	26589	CUACAGAAUAAUUGGGUG	1478	26607	CACCCAAUUAUUCUGUAG	3129
26607	GACUGGCGGAUUGCGAUU	1479	26607	GACUGGCGGAUUGCGAUU	1479	26625	AUUGCAUUCUCCGCCAGUC	3130
26625	UGCAUUGCUUGUAUUGUA	1480	26625	UGCAUUGCUUGUAUUGUA	1480	26643	UACAAUACAACCAUUGCA	3131
26643	AGGCUUGUUGGCUUAGC	1481	26643	AGGCUUGUUGGCUUAGC	1481	26661	GUAAAGCCACAUAAGCCU	3132
26661	CUACUUCGUUGCUUCCUUC	1482	26661	CUACUUCGUUGCUUCCUUC	1482	26679	GAAGGAAGCAACGAAGUAG	3133
26679	CAGGCUUUUGCUCGUACC	1483	26679	CAGGCUUUUGCUCGUACC	1483	26697	GGUACGAGCAACAGCCUG	3134
26697	CCGCUCAUUGUGUCAUUC	1484	26697	CCGCUCAUUGUGUCAUUC	1484	26715	GAUAGCCACAUGAGCGG	3135
26715	CAACCCAGAAACAACAUI	1485	26715	CAACCCAGAAACAACAUI	1485	26733	AUGUUUUGUUUCUGGUUG	3136
26733	UCUUCUCAUUGGCCUCUC	1486	26733	UCUUCUCAUUGGCCUCUC	1486	26751	GAGAGCCAUUUGAGGAAGA	3137
26751	CCGGGGCAUUAUUGUAGC	1487	26751	CCGGGGCAUUAUUGUAGC	1487	26769	GGUCACAAUUGUCCCGCGG	3138
26769	CAGACCGCUCAUUGAAAGU	1488	26769	CAGACCGCUCAUUGAAAGU	1488	26787	ACUUCUCCAUAGAGCGGUCUG	3139
26787	UGAACUUGUCAUUGGUGCU	1489	26787	UGAACUUGUCAUUGGUGCU	1489	26805	AGCACCAUUGACAAGUUA	3140
26805	UGUGAUCAUUCGUGGUCAC	1490	26805	UGUGAUCAUUCGUGGUCAC	1490	26823	GUGACCCAGAAUUGAUCACA	3141
26823	CUUGCGAAUGGCCGGACAC	1491	26823	CUUGCGAAUGGCCGGACAC	1491	26841	GUGUCCGGCCAUUCGCAAG	3142
26841	CUCCCUAGGGCGCUGUGAC	1492	26841	CUCCCUAGGGCGCUGUGAC	1492	26859	GUCACAGCGCCCUAGGGAG	3143
26859	CAUUAAGGACCUGCCAAA	1493	26859	CAUUAAGGACCUGCCAAA	1493	26877	UUUUGGCAGGUCCUUAUUG	3144
26877	AGAGAUCAUUGUGGCUACA	1494	26877	AGAGAUCAUUGUGGCUACA	1494	26895	UGUAGCCACAGUUGAUCUCU	3145
26895	AUCACGAACGCUUUCUUAU	1495	26895	AUCACGAACGCUUUCUUAU	1495	26913	AUAAGAAAGCUUUGUGAU	3146
26913	UUACAAUUAAGGAGCGUG	1496	26913	UUACAAUUAAGGAGCGUG	1496	26931	CGACGCUCCUAAUUAUUA	3147
26931	GCAGCGUUAAGGACUGAU	1497	26931	GCAGCGUUAAGGACUGAU	1497	26949	AUCAGUGCCUACACGUGC	3148
26949	UUCAGGUUUUGCUGCAUAC	1498	26949	UUCAGGUUUUGCUGCAUAC	1498	26967	GUUAGCAGCAAAACCUGAA	3149
26967	CAACCGCUACCGUAUUGGA	1499	26967	CAACCGCUACCGUAUUGGA	1499	26985	UCCAAUACGGUAGCGGUUG	3150
26985	AAACUUAUAAUUAUUAACA	1500	26985	AAACUUAUAAUUAUUAACA	1500	27003	UGUUAUUAUUAUUAUUA	3151
27003	AGACCAGCGCGUAGCAAC	1501	27003	AGACCAGCGCGUAGCAAC	1501	27021	GUUGCUACCGCGGUGGUCU	3152
27021	CGACAAUUAUUGCUUUGCUA	1502	27021	CGACAAUUAUUGCUUUGCUA	1502	27039	UAGCAAAAGCAUUAUUGUCG	3153
27039	AGUACAGUAAGUGACAACA	1503	27039	AGUACAGUAAGUGACAACA	1503	27057	UGUUGUACCUUACUGUACU	3154
27057	AGAUGUUUAUCUUGUUGA	1504	27057	AGAUGUUUAUCUUGUUGA	1504	27075	UCAACAAGUAGAAACAUCU	3155
27075	ACUUCAGGUUAACAUAAGC	1505	27075	ACUUCAGGUUAACAUAAGC	1505	27093	GCUAUUGUAACCCUGGAAGU	3156
27093	CAGAGAUUAUGAUUAUCAU	1506	27093	CAGAGAUUAUGAUUAUCAU	1506	27111	AUGAUAAUCAUUAUCUCUG	3157

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27111	UUAUGAGGACUUUCAGGAU	1507	27111	UUAUGAGGACUUUCAGGAU	1507	27129	AUCCUGAAAGUCCUCAUAA	3158
27129	UUGCUAUUUUGGAUUCUGA	1508	27129	UUGCUAUUUUGGAUUCUGA	1508	27147	UCAAGAUUCCAAUAGCAA	3159
27147	ACGUUAUAAUAGAUCAAU	1509	27147	ACGUUAUAAUAGAUCAAU	1509	27165	AUUGAACUUUUAUUAACGU	3160
27165	UAGUGAGACAAUUAUUAA	1510	27165	UAGUGAGACAAUUAUUAA	1510	27183	UUAAAAUUUGUCACUA	3161
27183	AGCCUCUAUAAGAGAA	1511	27183	AGCCUCUAUAAGAGAA	1511	27201	UUCUUCUUAUAGAGGCU	3162
27201	AUUUUCGGAGUUAUUA	1512	27201	AUUUUCGGAGUUAUUA	1512	27219	UCAUCUAUCCCGAAUAAU	3163
27219	AUGAAGAACCUAUGGAGUU	1513	27219	AUGAAGAACCUAUGGAGUU	1513	27237	AACUCCAUAGGUUUCU	3164
27237	UAGAUUAUCCAUAAACGA	1514	27237	UAGAUUAUCCAUAAACGA	1514	27255	UCGUUUUAUGGAUAAUCUA	3165
27255	AACAUGAAAAUUAUCUCU	1515	27255	AACAUGAAAAUUAUCUCU	1515	27273	AGAGAAUAAUUAUCUUAU	3166
27273	UUCUGACAUUUAUUAUUA	1516	27273	UUCUGACAUUUAUUAUUA	1516	27291	AUACAAUCAAUGUCAGGAA	3167
27291	UUUACAUUCUUGCGAGCUAU	1517	27291	UUUACAUUCUUGCGAGCUAU	1517	27309	AUAGCUCGCAAGAUUAUAA	3168
27309	UAUCACUAUCAGGAGUGUG	1518	27309	UAUCACUAUCAGGAGUGUG	1518	27327	CACACUCCUGAUAGUGAUA	3169
27327	GUUAGAGGUACGACUGUAC	1519	27327	GUUAGAGGUACGACUGUAC	1519	27345	GUACAGUCGUACCUUAAC	3170
27345	CUACUAAAAGAACCUUGCC	1520	27345	CUACUAAAAGAACCUUGCC	1520	27363	GGCAAGGUUCUUUUAUUAU	3171
27363	CCAUACAGGAACAUACGAGG	1521	27363	CCAUACAGGAACAUACGAGG	1521	27381	CCUGUAUUGUCCUGAUGG	3172
27381	GGCAAUUCCACCAUUAUAC	1522	27381	GGCAAUUCCACCAUUAUAC	1522	27399	GGUGAAUUGGUAUUAUGCC	3173
27399	CCUCUUGCUGACAAUAAU	1523	27399	CCUCUUGCUGACAAUAAU	1523	27417	AUUUAUUGUCAGCAAGAGG	3174
27417	UUUGCACUAACUUGCACUA	1524	27417	UUUGCACUAACUUGCACUA	1524	27435	UAGUGCAAGUUAUGCAA	3175
27435	AGCACACAUUUGCUUUG	1525	27435	AGCACACAUUUGCUUUG	1525	27453	CAAAAGCAAAGUGUGUCU	3176
27453	GCUGUGCUGAGCGUACUC	1526	27453	GCUGUGCUGAGCGUACUC	1526	27471	GAGUACCGUCAGCAACGC	3177
27471	CGACUAACCUAUCAGCUGC	1527	27471	CGACUAACCUAUCAGCUGC	1527	27489	GCAGCUGAUAGGUUAUGUCG	3178
27489	CGUGCAAGUACAGUUAUC	1528	27489	CGUGCAAGUACAGUUAUC	1528	27507	GUGAAACUGAUUUGCAGC	3179
27507	CCAAACUUAUUAUCAGAC	1529	27507	CCAAACUUAUUAUCAGAC	1529	27525	GUCUGAAGAAAGUUIUGG	3180
27525	CAAGAGGAGGUUAACAAG	1530	27525	CAAGAGGAGGUUAACAAG	1530	27543	CUUGUUAAGCCUCCUUG	3181
27543	GAGCUCUACUCGCCAUUU	1531	27543	GAGCUCUACUCGCCAUUU	1531	27561	AAAGUGGCGAGUAGAGCUC	3182
27561	UUUCUAUUGUUGCUGCUC	1532	27561	UUUCUAUUGUUGCUGCUC	1532	27579	GAGCAGCAACAUAGAGAA	3183
27579	CUAGAUUUUUAUUAUUAU	1533	27579	CUAGAUUUUUAUUAUUAU	1533	27597	AAAGUAUUAUUAUUAUUA	3184
27597	UGCUUACCAUUAAGAGAA	1534	27597	UGCUUACCAUUAAGAGAA	1534	27615	UUCUCUUAUUGGUGAAGCA	3185
27615	AAGACAGAAUUAUAGAGCU	1535	27615	AAGACAGAAUUAUAGAGCU	1535	27633	AGCUCAUUAUUAUUAUUA	3186
27633	UCACUUUAUUAUUAUUAU	1536	27633	UCACUUUAUUAUUAUUAU	1536	27651	UAGAAGUCAUUAUUAUUA	3187
27651	AUUUGUCUUUUUAAGCCUU	1537	27651	AUUUGUCUUUUUAAGCCUU	1537	27669	AAGGCUAAUUAAGCACAAU	3188
27669	UUCUGCUAUUCCUUGUUUU	1538	27669	UUCUGCUAUUCCUUGUUUU	1538	27687	AAAACAAGGAUUAAGCAGAA	3189
27687	UAUUAUUGCUUAUUAUUAU	1539	27687	UAUUAUUGCUUAUUAUUAU	1539	27705	AAUUAUUAUUAAGCAUUAU	3190
27705	UUUGUUUUUACUCUGAAAU	1540	27705	UUUGUUUUUACUCUGAAAU	1540	27723	AUUUCGAGUGAAUUAUUAU	3191
27723	UCCAGGAUCUUAAGAAACC	1541	27723	UCCAGGAUCUUAAGAAACC	1541	27741	GGUUCUUAUUAUUAUUAU	3192
27741	CUUGUACCAAAUUAUUAU	1542	27741	CUUGUACCAAAUUAUUAU	1542	27759	GUUUAAGCUUUAUUAUUAU	3193
27759	CGAACAUGAAACUUCUUAU	1543	27759	CGAACAUGAAACUUCUUAU	1543	27777	AUGAGAAGUUUAUUAUUAU	3194
27777	UUGUUUUUACUUAUUAUUA	1544	27777	UUGUUUUUACUUAUUAUUA	1544	27795	GAAUUAUUAUUAUUAUUA	3195
27795	CUCUAUGCAGUUAUUAUUA	1545	27795	CUCUAUGCAGUUAUUAUUA	1545	27813	CAUUAUUAUUAUUAUUAU	3196
27813	GCACUGUAGUACAGCGCUG	1546	27813	GCACUGUAGUACAGCGCUG	1546	27831	CAGCGCUUAUUAUUAUUA	3197
27831	GUGCAUCUUAUUAUUAUUA	1547	27831	GUGCAUCUUAUUAUUAUUA	1547	27849	UGAGGUUAUUAUUAUUAU	3198
27849	AUGUGCUUUAUUAUUAUUA	1548	27849	AUGUGCUUUAUUAUUAUUA	1548	27867	CAAGGAUCUUAUUAUUAU	3199

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27867	GUAAGGUACAAACACUAGGG	1549	27867	GUAAGGUACAAACACUAGGG	1549	27885	CCUAGUGUUGUACCUUAC	3200
27885	GGUAAUACUUAUAGCACUG	1550	27885	GGUAAUACUUAUAGCACUG	1550	27903	CAGUGCUAAAGUUAUACC	3201
27903	GCUUGGCUUUGGCUUACG	1551	27903	GCUUGGCUUUGGCUUACG	1551	27921	CUAGAGCACAAAGCCAGC	3202
27921	GGAAGGUUUUACCUUUUC	1552	27921	GGAAGGUUUUACCUUUUC	1552	27939	GAAAAGGUAACCUUUCC	3203
27939	CAUAGAUGGCACACUAGG	1553	27939	CAUAGAUGGCACACUAGG	1553	27957	CCAUAGUGGCCACUUAUG	3204
27957	GUUCAAACUAGCACACCUA	1554	27957	GUUCAAACUAGCACACCUA	1554	27975	UAGGUGUGCAUUGUUAAC	3205
27975	AAUGUUAUUAUUAACUGUC	1555	27975	AAUGUUAUUAUUAACUGUC	1555	27993	GACAGUUGAUAGUAAAUU	3206
27993	CAAGAUCCAGCUGGUGGUG	1556	27993	CAAGAUCCAGCUGGUGGUG	1556	28011	CACCACAGCUGGAUUCUG	3207
28011	GCGCUUAUAGCUAGGUGUU	1557	28011	GCGCUUAUAGCUAGGUGUU	1557	28029	AACACCUAGCUUAAAGCGC	3208
28029	UGGUACCUUAUUAAGGUG	1558	28029	UGGUACCUUAUUAAGGUG	1558	28047	GACCUUAUUAAGGUAACCA	3209
28047	CACCAAACUGCUGCAUUA	1559	28047	CACCAAACUGCUGCAUUA	1559	28065	UAAUUGCAGCAGUUGGUG	3210
28065	AGAGACGUACUUGUUGUUU	1560	28065	AGAGACGUACUUGUUGUUU	1560	28083	AAACAACAGUACGUCUCU	3211
28083	UUAUAUAACGAACAAAUU	1561	28083	UUAUAUAACGAACAAAUU	1561	28101	AUUUGUUGUUUAUUA	3212
28101	UAAAUGUCUGAUUAUGGA	1562	28101	UAAAUGUCUGAUUAUGGA	1562	28119	UCCAUUAUCAGACAUUUA	3213
28119	ACCCAAUCAAACCAACGU	1563	28119	ACCCAAUCAAACCAACGU	1563	28137	ACGUUGGUUUAUUGGGU	3214
28137	UAGUGCCCGCCGCAUUA	1564	28137	UAGUGCCCGCCGCAUUA	1564	28155	UGUAUUGGGGGGACUA	3215
28155	AUUUGGUGACCCACAGAU	1565	28155	AUUUGGUGACCCACAGAU	1565	28173	AUCUGUGGGUCCACCAAU	3216
28173	UUCAACUGACUUAACCCAG	1566	28173	UUCAACUGACUUAACCCAG	1566	28191	CUGGUUAUUGUCCAUUA	3217
28191	GAUUGAGGACCAUUGGG	1567	28191	GAUUGAGGACCAUUGGG	1567	28209	CCCAUUGGUCUCCAUUC	3218
28209	GGCAAGGCCAAACAGCGC	1568	28209	GGCAAGGCCAAACAGCGC	1568	28227	GCGCUGUUUUGGCCUUGCC	3219
28227	CCGACCCCAAGGUUACCC	1569	28227	CCGACCCCAAGGUUACCC	1569	28245	GGGUAACCUUGGGUCCG	3220
28245	CAUAUAUCUGGCUUUGG	1570	28245	CAUAUAUCUGGCUUUGG	1570	28263	CCAAGACGCAGUAUUAUG	3221
28263	GUUCACAGCUCUACUCAG	1571	28263	GUUCACAGCUCUACUCAG	1571	28281	CUGAGUGAGAGCUGUGAAC	3222
28281	GCAUGGCAAGGAGGAACUU	1572	28281	GCAUGGCAAGGAGGAACUU	1572	28299	AAGUUCUCCUUGCCAUUC	3223
28299	UAGAUUCCUUGAGGCGAG	1573	28299	UAGAUUCCUUGAGGCGAG	1573	28317	CUGGCCUCGAGGGAUUC	3224
28317	GGCGUUCUUAUACACACC	1574	28317	GGCGUUCUUAUACACACC	1574	28335	GGUGUUAUUGGAACGCC	3225
28335	CAUAUGUGGUCCAGAUAC	1575	28335	CAUAUGUGGUCCAGAUAC	1575	28353	GUCAUCUGGACCAUUAUG	3226
28353	CCAAUUGGCUACUACCGA	1576	28353	CCAAUUGGCUACUACCGA	1576	28371	UCGGUAGUAGCCAAUUGG	3227
28371	AAGAGCUACCCGACGAGUU	1577	28371	AAGAGCUACCCGACGAGUU	1577	28389	AACUCGUGGGUAGCUCUU	3228
28389	UCGUGGUGGUGACGGCAA	1578	28389	UCGUGGUGGUGACGGCAA	1578	28407	UUUGCCGUCACCCACCA	3229
28407	AUUGAAAGAGCUCAGCCCC	1579	28407	AUUGAAAGAGCUCAGCCCC	1579	28425	GGGCGUGAGCUCUUAUUA	3230
28425	CAGUUGGUUUAUUAUUA	1580	28425	CAGUUGGUUUAUUAUUA	1580	28443	GUAAUAGAAGUACCAUUG	3231
28443	CCUAGGAACUGGCCAGAA	1581	28443	CCUAGGAACUGGCCAGAA	1581	28461	UUCUGGCCAGUUCUAGG	3232
28461	AGCUUACUUCUUAUACGGC	1582	28461	AGCUUACUUCUUAUACGGC	1582	28479	CCGUGAGGAAGUAGGCU	3233
28479	CGCUAACAAGAGGCAUC	1583	28479	CGCUAACAAGAGGCAUC	1583	28497	GAUGCUUUAUUGUUAUGG	3234
28497	CGUAGGUGUUAUUAUUA	1584	28497	CGUAGGUGUUAUUAUUA	1584	28515	CUCAGUUGCAACCCAUACG	3235
28515	GGGAGCCUUAUUAUUA	1585	28515	GGGAGCCUUAUUAUUA	1585	28533	GGGUGUAUUAAGGCCUCC	3236
28533	CAAAGACCAUUAUUAUUA	1586	28533	CAAAGACCAUUAUUAUUA	1586	28551	GGUGCCAAUUGGCUUUAUG	3237
28551	CCGCAAUUAUUAUUAUUA	1587	28551	CCGCAAUUAUUAUUAUUA	1587	28569	AUUGUUAUUAAGGAUUGCGG	3238
28569	UGCUGCCACCGUGCUACAA	1588	28569	UGCUGCCACCGUGCUACAA	1588	28587	UUGUAGCACGGUGGCAGCA	3239
28587	ACUUCUUAAGGAACAACA	1589	28587	ACUUCUUAAGGAACAACA	1589	28605	UGUUGUCCUUAAGGAAGU	3240
28605	AUUGCCAAAGGCUUUAU	1590	28605	AUUGCCAAAGGCUUUAU	1590	28623	GUAGAAGCCUUAUUGGCAU	3241

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28623	CGCAGAGGGAAGCAGAGGC	1591	28623	CGCAGAGGGAAGCAGAGGC	1591	28641	GCCUCUGCUUCCUCUGCG	3242
28641	CGGCAGUCAAGCCUCUCU	1592	28641	CGGCAGUCAAGCCUCUCU	1592	28659	AGAAAGGCUUGACUGCCG	3243
28659	UGCUCUCUACACGUAU	1593	28659	UGCUCUCUACACGUAU	1593	28677	ACUACGUAUGAGGAGCGA	3244
28677	UCGCGGUAUUCAGAAU	1594	28677	UCGCGGUAUUCAGAAU	1594	28695	AUUUCUUAUUUACCGCGA	3245
28695	UUCAACUCCUGGCAGAGU	1595	28695	UUCAACUCCUGGCAGAGU	1595	28713	ACUGGCGCAGGAGUUGAA	3246
28713	UAGGGAAUUCUCCUGCU	1596	28713	UAGGGAAUUCUCCUGCU	1596	28731	AGCAGGAAUJUCCCCUA	3247
28731	UGAAUUGCUAGCGGAGU	1597	28731	UGAAUUGCUAGCGGAGU	1597	28749	ACCUCGCUAGCCAUUCGA	3248
28749	UGUGAAACUGCCUCGCG	1598	28749	UGUGAAACUGCCUCGCG	1598	28767	CGCGAGGCGAGUUACACCA	3249
28767	GCUAUUGCUAGACAGA	1599	28767	GCUAUUGCUAGACAGA	1599	28785	UCUGUCUAGCAGCAAUAGC	3250
28785	AUUGAACCCAGCUAGAGC	1600	28785	AUUGAACCCAGCUAGAGC	1600	28803	GCUCUACAGCUGGUCAAU	3251
28803	CAAAGUUUCUGGUAAGGC	1601	28803	CAAAGUUUCUGGUAAGGC	1601	28821	GCCUUUACCAAGAAUUG	3252
28821	CCAACAACAAGGCCAA	1602	28821	CCAACAACAAGGCCAA	1602	28839	UUGGCCUUGUUGUUGG	3253
28839	AACUGUCACUAGAAUUCU	1603	28839	AACUGUCACUAGAAUUCU	1603	28857	AGAUUUCUUGAGACAGUU	3254
28857	UGCUGCUGAGGCUAAU	1604	28857	UGCUGCUGAGGCUAAU	1604	28875	UUUAGAUCCUCAGCAGCA	3255
28875	AAAGCCUCGCCAAAACGU	1605	28875	AAAGCCUCGCCAAAACGU	1605	28893	ACGUUUUUGCGGAGGUUU	3256
28893	UACUGCCACAAAACAGUAC	1606	28893	UACUGCCACAAAACAGUAC	1606	28911	GUACUGUUUUGUGGAGUA	3257
28911	CAACGUCACUAGCAUUU	1607	28911	CAACGUCACUAGCAUUU	1607	28929	AAUUGCUUGAGUGACGUUG	3258
28929	UGGAGACGUGGUCCAGAA	1608	28929	UGGAGACGUGGUCCAGAA	1608	28947	UUCUGGACACGUCUCCCA	3259
28947	ACAAACCCAAAGAAUUC	1609	28947	ACAAACCCAAAGAAUUC	1609	28965	GAAUUCUUGGUGUUUGU	3260
28965	CGGGACCAAGACCUAUUC	1610	28965	CGGGACCAAGACCUAUUC	1610	28983	GAUUAAGGUGUUGUCCCG	3261
28983	CAGACAAGGAACUAGUAC	1611	28983	CAGACAAGGAACUAGUAC	1611	29001	GUAAUCGUUCCUUGUCUG	3262
29001	CAACAUIUGCCGCAAAU	1612	29001	CAACAUIUGCCGCAAAU	1612	29019	AUUUGCGGCAAAUUGUUG	3263
29019	UGACAUIUGCUCUCCAGU	1613	29019	UGACAUIUGCUCUCCAGU	1613	29037	ACUUGGAGCAAAUUGUCA	3264
29037	UGCCUCUGCAUUCUUUGGA	1614	29037	UGCCUCUGCAUUCUUUGGA	1614	29055	UCCAAAGAAUGCAGAGGCA	3265
29055	AAUGUCACGUAUUGGCAUG	1615	29055	AAUGUCACGUAUUGGCAUG	1615	29073	CAUGCAAUGCGUGACAUU	3266
29073	GGAAGUCACACCUUGGGA	1616	29073	GGAAGUCACACCUUGGGA	1616	29091	UCCCGAAGGUGUGACUUC	3267
29091	AACAUGGCGACUUAUUAU	1617	29091	AACAUGGCGACUUAUUAU	1617	29109	AUGAAAGUCAGCCAUUUG	3268
29109	UGGAGCCAUUAUUAUUGGAU	1618	29109	UGGAGCCAUUAUUAUUGGAU	1618	29127	AUCCAAUUUAUUGGCUCCA	3269
29127	UGACAAAGAUCCACAAUUC	1619	29127	UGACAAAGAUCCACAAUUC	1619	29145	GAAUUGGGAUCCUUGUCA	3270
29145	CAAAGACAACGUAUUAUUG	1620	29145	CAAAGACAACGUAUUAUUG	1620	29163	CAGUAUGAGCUUGUCUUUG	3271
29163	GCUGAACAAAGCACAUAUAC	1621	29163	GCUGAACAAAGCACAUAUAC	1621	29181	GUCAUUGUGCUUGUUCAGC	3272
29181	CGCAUACAAACAUUCCCA	1622	29181	CGCAUACAAACAUUCCCA	1622	29199	UGGGAUUGUUUUGUAUGCG	3273
29199	ACCAACAGAGCCUAAAAAG	1623	29199	ACCAACAGAGCCUAAAAAG	1623	29217	CUUUUAGGCUUGUUGGU	3274
29217	GGACAAAAGAAAAGACU	1624	29217	GGACAAAAGAAAAGACU	1624	29235	AGUCUUUUUUUUUUGUCC	3275
29235	UGAUGAAGCUCAGCCUUG	1625	29235	UGAUGAAGCUCAGCCUUG	1625	29253	CAAAGGCUAGCUUAUCA	3276
29253	GCCGAGAGACAAAAGAG	1626	29253	GCCGAGAGACAAAAGAG	1626	29271	CUUCUUUUGUCUCUGCGGC	3277
29271	GACGCCACUGUGACUCUU	1627	29271	GACGCCACUGUGACUCUU	1627	29289	AAGAGUCACAGUGGCGUGC	3278
29289	UCUCCUCGCGGUGACAU	1628	29289	UCUCCUCGCGGUGACAU	1628	29307	CAUGUGCCGCGAGGAAGA	3279
29307	GGAUGAUUUCUCCAGACAA	1629	29307	GGAUGAUUUCUCCAGACAA	1629	29325	UUGUCUGGAGAAAUCAUCC	3280
29325	ACUUCAAAUIUCCAGAGU	1630	29325	ACUUCAAAUIUCCAGAGU	1630	29343	ACUUCAGGAAUUUUGAAGU	3281
29343	UGGAGCUUCUGUGAUUCA	1631	29343	UGGAGCUUCUGUGAUUCA	1631	29361	UGAAUCAGCAGAAAGCUCCA	3282
29361	AACUCAGGCAUAAACACUC	1632	29361	AACUCAGGCAUAAACACUC	1632	29379	GAGUGUUUAUGCCUGAGUU	3283

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29379	CAUGAUGACCACACAAGGC	1633	29379	CAUGAUGACCACACAAGGC	1633	29397	GCCUUGUGUGUCAUCAUG	3284
29397	CAGAUGGGCUAUGUAAACG	1634	29397	CAGAUGGGCUAUGUAAACG	1634	29415	CGUUUACAUAGCCCAUCUG	3285
29415	GUUUUCGCAUUCCGUUUA	1635	29415	GUUUUCGCAUUCCGUUUA	1635	29433	UAAACGGAAUUGCGAAAC	3286
29433	ACGAUACAUAGUCUACUCU	1636	29433	ACGAUACAUAGUCUACUCU	1636	29451	AGAGUAGACUAGUUAUCGU	3287
29451	UUUGGCAGAAUGAAUUCUC	1637	29451	UUUGGCAGAAUGAAUUCUC	1637	29469	GAGAAUUCUUCUGCACAA	3288
29469	CGUAAUAACAGCACAAAG	1638	29469	CGUAAUAACAGCACAAAG	1638	29487	CUUGGUCUGUUUAGUUACG	3289
29487	GUAGGUUUAGUUAAUUA	1639	29487	GUAGGUUUAGUUAAUUA	1639	29505	UAAAGUUAAUAACCCUAC	3290
29505	AAUCACAUAGCAUUCU	1640	29505	AAUCACAUAGCAUUCU	1640	29523	AAGAUUGCUAUGUGAGAUU	3291
29523	UUAAUCAAUGUGUAAUUA	1641	29523	UUAAUCAAUGUGUAAUUA	1641	29541	AUUGUACACAUUGAUUAA	3292
29541	UAGGGAGGACUUUAAAGAG	1642	29541	UAGGGAGGACUUUAAAGAG	1642	29559	CUCUUCAAGUCCUCCUA	3293
29559	GCCACCACAUUUUUAUCGA	1643	29559	GCCACCACAUUUUUAUCGA	1643	29577	UCGAUGAAAUGUGGUGGC	3294
29577	AGGCCACGCGGAGUACGAU	1644	29577	AGGCCACGCGGAGUACGAU	1644	29595	AUCGUACUCCGUGGCGCU	3295
29595	UCGAGGUAACAGUGAAUAA	1645	29595	UCGAGGUAACAGUGAAUAA	1645	29613	UUUUUACUAGUCCUCCGA	3296
29613	AUGCUAGGGAGAGUCCU	1646	29613	AUGCUAGGGAGAGUCCU	1646	29631	AGGCAGCUCUCCUAGCAU	3297
29631	UAUAUGGAAGAGCCCUAAU	1647	29631	UAUAUGGAAGAGCCCUAAU	1647	29649	AUUAGGGCUCUCCCAUUA	3298
29649	UGUGUAAAUAUUUUUAG	1648	29649	UGUGUAAAUAUUUUUAG	1648	29667	CUAAAUAUUUUUACACA	3299
29667	GUAGUGCUAUCCCAUGUG	1649	29667	GUAGUGCUAUCCCAUGUG	1649	29685	CACAUGGGGAUAGCACUAC	3300
29685	GAUUUUAAUAGCUUCUAG	1650	29685	GAUUUUAAUAGCUUCUAG	1650	29703	CUAAGAAGCUAUUAAAUC	3301
29703	GGAGAAUGACAAAAA	1651	29703	GGAGAAUGACAAAAA	1651	29721	UUUUUUUUUGUCAUUCUCC	3302

The 3'-ends of the Upper sequence and the Lower sequence of the siNA construct can include an overhang sequence, for example about 1, 2, 3, or 4 nucleotides in length, preferably 2 nucleotides in length, wherein the overhanging sequence of the lower sequence is optionally complementary to a portion of the target sequence. The overhang can comprise the general structure B, BNN, NN, BNsN, or NsN, where B stands for any terminal cap moiety, N stands for any nucleotide (e.g., thymidine) and s stands for phosphorothioate or other internucleotide linkage as described herein (e.g. internucleotide linkage having Formula I). The upper sequence is also referred to as the sense strand, whereas the lower sequence is also referred to as the antisense strand. The upper and lower sequences in the Table can further comprise a chemical modification having Formulae I-VII or any combination thereof (see for example chemical modifications as shown in Table V herein).

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Table III: SARS synthetic siRNA and Target Sequences

Target Pos	Target	SeqID	RPI#	Aliases	Sequence	SeqID
1655	UGAAUGAAGAGGUUGCCCAUCAUU	3303		SARS:1657U21 siRNA sense	AUUGAAGAGGUUGCCCAUCATT	3311
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1166U21 siRNA sense	UUGCAUCUCCACAGGAGUATT	3312
2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2383U21 siRNA sense	CAAAGCAAGGGACUUUACCTT	3313
2598	CUGUGUAAUUGGCCUCAUGCUCU	3306		SARS:2600U21 siRNA sense	GUGUAAUUGGCCUCAUGCUTT	3314
26572	UUUGUCUUUGCUGCUGUCUACAG	3307		SARS:26574U21 siRNA sense	UGUGCUUGCUGCUGUCUACTT	3315
26790	ACUUGUCAUUUGGUGCUGUGAUA	3308		SARS:26792U21 siRNA sense	UUGUCAUUUGGUGCUGUGAATT	3316
28786	UUGAACCAAGCUUGAGAGCAAAGU	3309		SARS:28788U21 siRNA sense	GAACCAAGCUUGAGAGCAAATT	3317
26529	GCUUGUUUUCCUCUGGCUCUUGU	3310		SARS:26531U21 siRNA sense	UUGUUUUCCUCUGGCUCUUTT	3318
1655	UGAAUGAAGAGGUUGCCCAUCAUU	3303		SARS:1675L21 siRNA (1657C) antisense	UGAUGGCAACCCUCUUCAUUTT	3319
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1184L21 siRNA (1166C) antisense	CACUCCUGUGGAGAUCCAATT	3320
2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2401L21 siRNA (2383C) antisense	GGUAAAGUCCCUUGCUUUUGTT	3321
2598	CUGUGUAAUUGGCCUCAUGCUCU	3306		SARS:2618L21 siRNA (2600C) antisense	AGCAUGAGGCCAUUUUACACTT	3322
26572	UUUGUCUUUGCUGCUGUCUACAG	3307		SARS:26592L21 siRNA (26574C) antisense	GUAGACAGCAGCAAGCACATT	3323
26790	ACUUGUCAUUUGGUGCUGUGAUA	3308		SARS:26810L21 siRNA (26792C) antisense	AUCACAGCACCAUAUGACAATT	3324
28786	UUGAACCAAGCUUGAGAGCAAAGU	3309		SARS:28806L21 siRNA (28788C) antisense	UUUGCUCUCAAGCUGGUUCTT	3325
26529	GCUUGUUUUCCUCUGGCUCUUGU	3310		SARS:26549L21 siRNA (26531C) antisense	AAGAGCCAGAGGAAACAATT	3326
1655	UGAAUGAAGAGGUUGCCCAUCAUU	3303		SARS:1657U21 siRNA stab04 sense	B AAUGAAGAGGUUGCCCAUCATT B	3327
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1166U21 siRNA stab04 sense	B uuGcAuccccAcAGGAGUATT B	3328
2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2383U21 siRNA stab04 sense	B cAAAGcAAGGGAcuuuAccTT B	3329
2598	CUGUGUAAUUGGCCUCAUGCUCU	3306		SARS:2600U21 siRNA stab04 sense	B GuGuAAAUuGGccuAuGcuTT B	3330
26572	UUUGUCUUUGCUGCUGUCUACAG	3307		SARS:26574U21 siRNA stab04 sense	B uGuGcuuGcuGcuGucuAcTT B	3331
26790	ACUUGUCAUUUGGUGCUGUGAUA	3308		SARS:26792U21 siRNA stab04 sense	B uuGuCAuuGGGuGuGuGuGauTT B	3332
28786	UUGAACCAAGCUUGAGAGCAAAGU	3309		SARS:28788U21 siRNA stab04 sense	B GAAccAGcuuGAGAGcAAATT B	3333
26529	GCUUGUUUUCCUCUGGCUCUUGU	3310		SARS:26531U21 siRNA stab04 sense	B uuGuuuuccucuGGcucuTT B	3334
1655	UGAAUGAAGAGGUUGCCCAUCAUU	3303		SARS:1675L21 siRNA (1657C) stab05 antisense	uGAUGGcAAccuccuAuTsT	3335
1164	UGUUGCAUCUCCACAGGAGUGUA	3304		SARS:1184L21 siRNA (1166C) stab05 antisense	cAcuccuGuGGAGAUcGAATsT	3336

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2381	CUCAAAGCAAGGGACUUUACCGU	3305	SARS:2401L21 siRNA (2383C) slab05 antisense	GGUAAAAGuccuuGcuuGTsT	3337
2598	CUGUGUAAUUGGCCUCAUGCUCU	3306	SARS:2618L21 siRNA (2600C) slab05 antisense	AGcAuGAGGccAuuuAcATsT	3338
26572	UUUGUGCUUGCUGCUGUCUACAG	3307	SARS:26592L21 siRNA (26574C) slab05 antisense	GUAGAcAGcAGcAAAGcAcATsT	3339
26790	ACUUGUCAUUGGUGCUGUGAUA	3308	SARS:26810L21 siRNA (26792C) slab05 antisense	AucAcAGcAccAAuAGAcAAATsT	3340
28786	UUGAACcAGCUUGAGAGCAAAGU	3309	SARS:28806L21 siRNA (28788C) slab05 antisense	uuuGcuucAAAGcuGGuucTsT	3341
26529	GCUUGUUUCCUCUGGCUCUUGU	3310	SARS:26549L21 siRNA (26531C) slab05 antisense	AAGAGccAGAGGAAAAcAAATsT	3342
1655	UGAAUGAAGAGGUUGCCAUCAUU	3303	SARS:1657U21 siRNA slab07 sense	B AAUGAAAGAGGUuGccAucATT B	3343
1164	UGUUGCAUCUCCACAGGAGUGUA	3304	SARS:1166U21 siRNA slab07 sense	B uuGcAucuccAcAGGAGuGTT B	3344
2381	CUCAAAGCAAGGGACUUUACCGU	3305	SARS:2383U21 siRNA slab07 sense	B cAAAAGcAAAGGGAGcuuAccTT B	3345
2598	CUGUGUAAUUGGCCUCUACAG	3306	SARS:2600U21 siRNA slab07 sense	B GuGuAAAUuGGccucAuGcuTT B	3346
26572	UUUGUGCUUGCUGCUGUCUACAG	3307	SARS:26574U21 siRNA slab07 sense	B uGuGcuuGcuGcuGucuAcTT B	3347
26790	ACUUGUCAUUGGUGCUGUGAUA	3308	SARS:26792U21 siRNA slab07 sense	B uuGucAuuuGuGuGuGauTT B	3348
28786	UUGAACcAGCUUGAGAGCAAAGU	3309	SARS:28788U21 siRNA slab07 sense	B GAACcAGcuuGAGAGcAAATTT B	3349
26529	GCUUGUUUCCUCUGGCUCUUGU	3310	SARS:26531U21 siRNA slab07 sense	B uuGuuuuccuGccuucTT B	3350
1655	UGAAUGAAGAGGUUGCCAUCAUU	3303	SARS:1675L21 siRNA (1657C) slab11 antisense	UGAuGGcAAccuucAuutTsT	3351
1164	UGUUGCAUCUCCACAGGAGUGUA	3304	SARS:1184L21 siRNA (1166C) slab11 antisense	cAcuccuGuGGAGAuGcAAATsT	3352
2381	CUCAAAGCAAGGGACUUUACCGU	3305	SARS:2401L21 siRNA (2383C) slab11 antisense	GGUAAAAGuccuuGcuuGTsT	3353
2598	CUGUGUAAUUGGCCUCAUGCUCU	3306	SARS:2618L21 siRNA (2600C) slab11 antisense	AGcAuGAGGccAuuuAcATsT	3354
26572	UUUGUGCUUGCUGCUGUCUACAG	3307	SARS:26592L21 siRNA (26574C) slab11 antisense	GuAGAcAGcAGcAAAGcAcATsT	3355
26790	ACUUGUCAUUGGUGCUGUGAUA	3308	SARS:26810L21 siRNA (26792C) slab11 antisense	AucAcAGcAccAAuAGAcAAATsT	3356
28786	UUGAACcAGCUUGAGAGCAAAGU	3309	SARS:28806L21 siRNA (28788C) slab11 antisense	uuuGcuucAAAGcuGGuucTsT	3357
26529	GCUUGUUUCCUCUGGCUCUUGU	3310	SARS:26549L21 siRNA (26531C) slab11 antisense	AAGAGccAGAGGAAAAcAAATsT	3358
1655	UGAAUGAAGAGGUUGCCAUCAUU	3303	SARS:1657U21 siRNA slab08 sense	AAUGAAGAGGUuGccAucATsT	3359
1164	UGUUGCAUCUCCACAGGAGUGUA	3304	SARS:1166U21 siRNA slab08 sense	uuGcAucuccAcAGGAGuGTsT	3360
2381	CUCAAAGCAAGGGACUUUACCGU	3305	SARS:2383U21 siRNA slab08 sense	cAAAGcAAAGGGAGcuuAccTsT	3361
2598	CUGUGUAAUUGGCCUCAUGCUCU	3306	SARS:2600U21 siRNA slab08 sense	GuGuAAAUuGGccucAuGcuTsT	3362

(400/110_US)

26572	UUUGUCUUGCUGCUGUCUACAG	3307		SARS:26574U21 siRNA stab08 sense	uGuGcuuGcuGcuGucAcTsT	3363
26790	ACUUGUCAUUGGUGCUGUGAUA	3308		SARS:26792U21 siRNA stab08 sense	uuGucAuuGGuGcuGuGAuTsT	3364
28786	UUGAACAGCUUGAGAGCAAAGU	3309		SARS:28788U21 siRNA stab08 sense	GAAccAGcuuGAGAGcAAATsT	3365
26529	GCUUGUUUCCUCUGGCUCUUGU	3310		SARS:26531U21 siRNA stab08 sense	uuGuuuuccucuGGcucuTsT	3366
1655	UGAAUGAAGAGGUUGCCAUAUU	3303		SARS:1675L21 siRNA (1657C) stab08 antisense	uGAuGGcAAccucuucAuuTsT	3367
1164	UGUUGCAUCCACAGGAGUGUA	3304		SARS:1184L21 siRNA (1166C) stab08 antisense	cAcuccuGuGGAGAuGcAAATsT	3368
2381	CUCAAAGCAAGGGACUUUACCGU	3305		SARS:2401L21 siRNA (2383C) stab08 antisense	GGuAAAGucccuuGcuuGTsT	3369
2598	CUGUGUAAUUGGCCUCAUGCUCU	3306		SARS:2618L21 siRNA (2600C) stab08 antisense	AGcAuGAGGGccAuuuAcAcTsT	3370
26572	UUUGUCUUGCUGCUGUCUACAG	3307		SARS:26592L21 siRNA (26574C) stab08 antisense	GuAGAcAGcAGcAAGGcAcTsT	3371
26790	ACUUGUCAUUGGUGCUGUGAUA	3308		SARS:26810L21 siRNA (26792C) stab08 antisense	AucACAGcAccAAuGAcAAATsT	3372
28786	UUGAACCAAGCUUGAGAGCAAAGU	3309		SARS:28806L21 siRNA (28788C) stab08 antisense	uuuGcucucAAAGcuGGuucTsT	3373
26529	GCUUGUUUCCUCUGGCUCUUGU	3310		SARS:26549L21 siRNA (26531C) stab08 antisense	AAGAGccAGAGGAAAAcAAATsT	3374

Uppercase = ribonucleotide
u,c = 2'-deoxy-2'-fluoro U, C
A = 2'-O-methyl Adenosine
G = 2'-O-methyl Guanosine
T = thymidine
B = inverted deoxy abasic
s = phosphorothioate linkage
A = deoxy Adenosine
G = deoxy Guanosine

Table IV

Non-limiting examples of Stabilization Chemistries for chemically modified siNA constructs

Chemistry	pyrimidine	Purine	cap	p=S	Strand
"Stab 00"	Ribo	Ribo	TT at 3'-ends		S/AS
"Stab 1"	Ribo	Ribo	-	5 at 5'-end 1 at 3'-end	S/AS
"Stab 2"	Ribo	Ribo	-	All linkages	Usually AS
"Stab 3"	2'-fluoro	Ribo	-	4 at 5'-end 4 at 3'-end	Usually S
"Stab 4"	2'-fluoro	Ribo	5' and 3'-ends	-	Usually S
"Stab 5"	2'-fluoro	Ribo	-	1 at 3'-end	Usually AS
"Stab 6"	2'-O-Methyl	Ribo	5' and 3'-ends	-	Usually S
"Stab 7"	2'-fluoro	2'-deoxy	5' and 3'-ends	-	Usually S
"Stab 8"	2'-fluoro	2'-O-Methyl	-	1 at 3'-end	Usually AS
"Stab 9"	Ribo	Ribo	5' and 3'-ends	-	Usually S
"Stab 10"	Ribo	Ribo	-	1 at 3'-end	Usually AS
"Stab 11"	2'-fluoro	2'-deoxy	-	1 at 3'-end	Usually AS
"Stab 12"	2'-fluoro	LNA	5' and 3'-ends		Usually S
"Stab 13"	2'-fluoro	LNA		1 at 3'-end	Usually AS
"Stab 14"	2'-fluoro	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 15"	2'-deoxy	2'-deoxy		2 at 5'-end 1 at 3'-end	Usually AS
"Stab 16"	Ribo	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 17"	2'-O-Methyl	2'-O-Methyl	5' and 3'-ends		Usually S
"Stab 18"	2'-fluoro	2'-O-Methyl	5' and 3'-ends	1 at 3'-end	Usually S
"Stab 19"	2'-fluoro	2'-O-Methyl	3'-end		Usually AS
"Stab 20"	2'-fluoro	2'-deoxy	3'-end		Usually AS
"Stab 21"	2'-fluoro	Ribo	3'-end		Usually AS
"Stab 22"	Ribo	Ribo	3'-end -		Usually AS

CAP = any terminal cap, see for example Figure 10.

All Stab 1-22 chemistries can comprise 3'-terminal thymidine (TT) residues

All Stab 1-22 chemistries typically comprise about 21 nucleotides, but can vary as described herein.

S = sense strand

AS = antisense strand

Table V

A. 2.5 μ mol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	6.5	163 μ L	45 sec	2.5 min	7.5 min
S-Ethyl Tetrazole	23.8	238 μ L	45 sec	2.5 min	7.5 min
Acetic Anhydride	100	233 μ L	5 sec	5 sec	5 sec
N-Methyl Imidazole	186	233 μ L	5 sec	5 sec	5 sec
TCA	176	2.3 mL	21 sec	21 sec	21 sec
Iodine	11.2	1.7 mL	45 sec	45 sec	45 sec
Beaucage	12.9	645 μ L	100 sec	300 sec	300 sec
Acetonitrile	NA	6.67 mL	NA	NA	NA

B. 0.2 μ mol Synthesis Cycle ABI 394 Instrument

Reagent	Equivalents	Amount	Wait Time* DNA	Wait Time* 2'-O-methyl	Wait Time*RNA
Phosphoramidites	15	31 μ L	45 sec	233 sec	465 sec
S-Ethyl Tetrazole	38.7	31 μ L	45 sec	233 min	465 sec
Acetic Anhydride	655	124 μ L	5 sec	5 sec	5 sec
N-Methyl Imidazole	1245	124 μ L	5 sec	5 sec	5 sec
TCA	700	732 μ L	10 sec	10 sec	10 sec
Iodine	20.6	244 μ L	15 sec	15 sec	15 sec
Beaucage	7.7	232 μ L	100 sec	300 sec	300 sec
Acetonitrile	NA	2.64 mL	NA	NA	NA

C. 0.2 μ mol Synthesis Cycle 96 well Instrument

Reagent	Equivalents:DNA/ 2'-O-methyl/Ribo	Amount: DNA/2'-O- methyl/Ribo	Wait Time* DNA	Wait Time* 2'-O- methyl	Wait Time* Ribo
Phosphoramidites	22/33/66	40/60/120 μ L	60 sec	180 sec	360sec
S-Ethyl Tetrazole	70/105/210	40/60/120 μ L	60 sec	180 min	360 sec
Acetic Anhydride	265/265/265	50/50/50 μ L	10 sec	10 sec	10 sec
N-Methyl Imidazole	502/502/502	50/50/50 μ L	10 sec	10 sec	10 sec
TCA	238/475/475	250/500/500 μ L	15 sec	15 sec	15 sec
Iodine	6.8/6.8/6.8	80/80/80 μ L	30 sec	30 sec	30 sec
Beaucage	34/51/51	80/120/120	100 sec	200 sec	200 sec
Acetonitrile	NA	1150/1150/1150 μ L	NA	NA	NA

- 5
- Wait time does not include contact time during delivery.
 - Tandem synthesis utilizes double coupling of linker molecule

CLAIMS

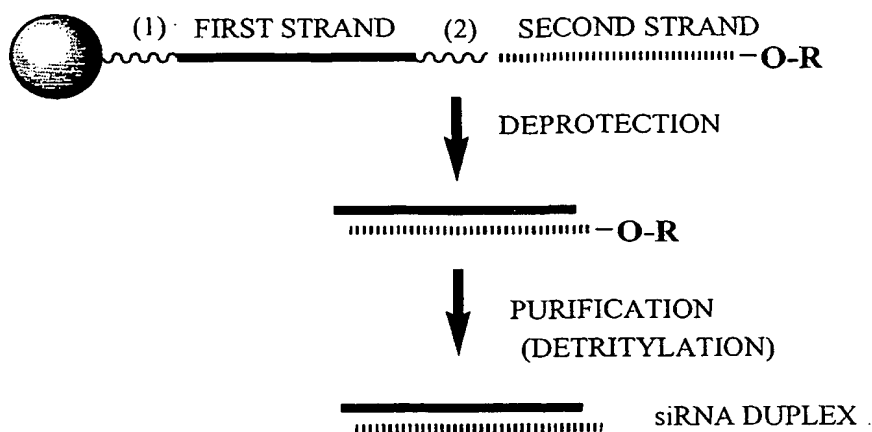
What we claim is:

1. A chemically synthesized double stranded short interfering nucleic acid (siNA) molecule that directs cleavage of a severe acute respiratory syndrome (SARS) virus RNA via RNA interference, wherein:
 - a. each strand of said siNA molecule is about 19 to about 23 nucleotides in length;
 - b. one strand of said siNA molecule comprises nucleotide sequence having sufficient complementarity to said SARS virus RNA for the siNA molecule to direct cleavage of the SARS virus RNA via RNA interference; and
 - c. said siNA molecule does not require the presence of nucleotides having a 2'-hydroxy group for mediating RNA interference.
2. The siNA molecule of claim 1, wherein said siNA molecule comprises no ribonucleotides.
3. The siNA molecule of claim 1, wherein said siNA molecule comprises ribonucleotides.
4. The siNA molecule of claim 1, wherein one strand of said double-stranded siNA molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of a SARS virus gene or a portion thereof, and wherein a second strand of said double-stranded siNA molecule comprises a nucleotide sequence substantially similar to the nucleotide sequence or a portion thereof of said SARS virus RNA.
5. The siNA molecule of claim 4, wherein each strand of the siNA molecule comprises about 19 to about 23 nucleotides, and wherein each strand comprises at least about 19 nucleotides that are complementary to the nucleotides of the other strand.
6. The siNA molecule of claim 1, wherein said siNA molecule comprises an antisense region comprising a nucleotide sequence that is complementary to a nucleotide sequence of a SARS virus gene or a portion thereof, and wherein said siNA further comprises a sense region, wherein said sense region comprises a nucleotide sequence substantially similar to the nucleotide sequence of said SARS virus gene or a portion thereof.

7. The siNA molecule of claim 6, wherein said antisense region and said sense region comprises about 19 to about 23 nucleotides, and wherein said antisense region comprises at least about 19 nucleotides that are complementary to nucleotides of the sense region.
- 5 8. The siNA molecule of claim 1, wherein said siNA molecule comprises a sense region and an antisense region, and wherein said antisense region comprises a nucleotide sequence that is complementary to a nucleotide sequence of RNA encoded by a SARS virus gene, or a portion thereof, and said sense region comprises a nucleotide sequence that is complementary to said antisense region.
- 10 9. The siNA molecule of claim 6, wherein said siNA molecule is assembled from two separate oligonucleotide fragments wherein one fragment comprises the sense region and a second fragment comprises the antisense region of said siNA molecule.
10. The siNA molecule of claim claim 6, wherein said sense region is connected to the antisense region via a linker molecule.
- 15 11. The siNA molecule of claim 10, wherein said linker molecule is a polynucleotide linker.
12. The siNA molecule of claim 10, wherein said linker molecule is a non-nucleotide linker.
13. The siNA molecule of claim 6, wherein pyrimidine nucleotides in the sense region are 2'-O-methyl pyrimidine nucleotides.
- 20 14. The siNA molecule of claim 6, wherein purine nucleotides in the sense region are 2'-deoxy purine nucleotides.
15. The siNA molecule of claim 6, wherein pyrimidine nucleotides present in the sense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides.
- 25 16. The siNA molecule of claim 9, wherein the fragment comprising said sense region includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the fragment comprising said sense region.
17. The siNA molecule of claim 16, wherein said terminal cap moiety is an inverted deoxy abasic moiety.
- 30 18. The siNA molecule of claim 6, wherein pyrimidine nucleotides of said antisense region are 2'-deoxy-2'-fluoro pyrimidine nucleotides

19. The siNA molecule of claim 6, wherein purine nucleotides of said antisense region are 2'-O-methyl purine nucleotides.
20. The siNA molecule of claim 6, wherein purine nucleotides present in said antisense region comprise 2'-deoxy- purine nucleotides.
- 5 21. The siNA molecule of claim 18, wherein said antisense region comprises a phosphorothioate internucleotide linkage at the 3' end of said antisense region.
22. The siNA molecule of claim 6, wherein said antisense region comprises a glyceryl modification at the 3' end of said antisense region.
- 10 23. The siNA molecule of claim 9, wherein each of the two fragments of said siNA molecule comprise 21 nucleotides.
24. The siNA molecule of claim 23, wherein about 19 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule and wherein at least two 3' terminal nucleotides of each fragment of the siNA molecule are not base-paired to the nucleotides of the other
15 fragment of the siNA molecule.
25. The siNA molecule of claim 24, wherein each of the two 3' terminal nucleotides of each fragment of the siNA molecule are 2'-deoxy-pyrimidines.
26. The siNA molecule of claim 25, wherein said 2'-deoxy-pyrimidine is 2'-deoxy-thymidine.
- 20 27. The siNA molecule of claim 23, wherein all 21 nucleotides of each fragment of the siNA molecule are base-paired to the complementary nucleotides of the other fragment of the siNA molecule.
28. The siNA molecule of claim 23, wherein about 19 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoded by a SARS virus gene or a portion thereof.
25
29. The siNA molecule of claim 23, wherein 21 nucleotides of the antisense region are base-paired to the nucleotide sequence of the RNA encoded by a SARS virus gene or a portion thereof.
30. The siNA molecule of claim 9, wherein the 5'-end of the fragment comprising said
30 antisense region optionally includes a phosphate group.

31. A pharmaceutical composition comprising the siNA molecule of claim 1 in an acceptable carrier or diluent.

Figure 1

= SOLID SUPPORT

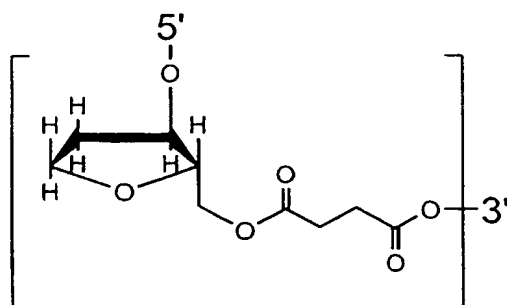
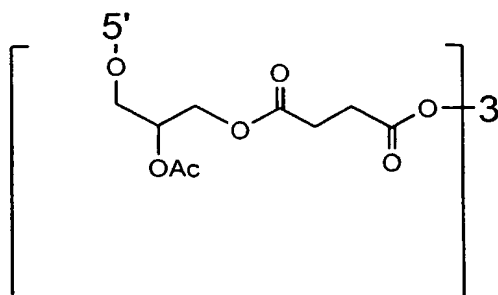
R = TERMINAL PROTECTING GROUP

FOR EXAMPLE:

DIMETHOXYTRITYL (DMT)

(1) = CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR
INVERTED DEOXYABASIC SUCCINATE)

(2) = CLEAVABLE LINKER
(FOR EXAMPLE: NUCLEOTIDE SUCCINATE OR
INVERTED DEOXYABASIC SUCCINATE)

INVERTED DEOXYABASIC SUCCINATE
LINKAGE

GLYCERYL SUCCINATE LINKAGE

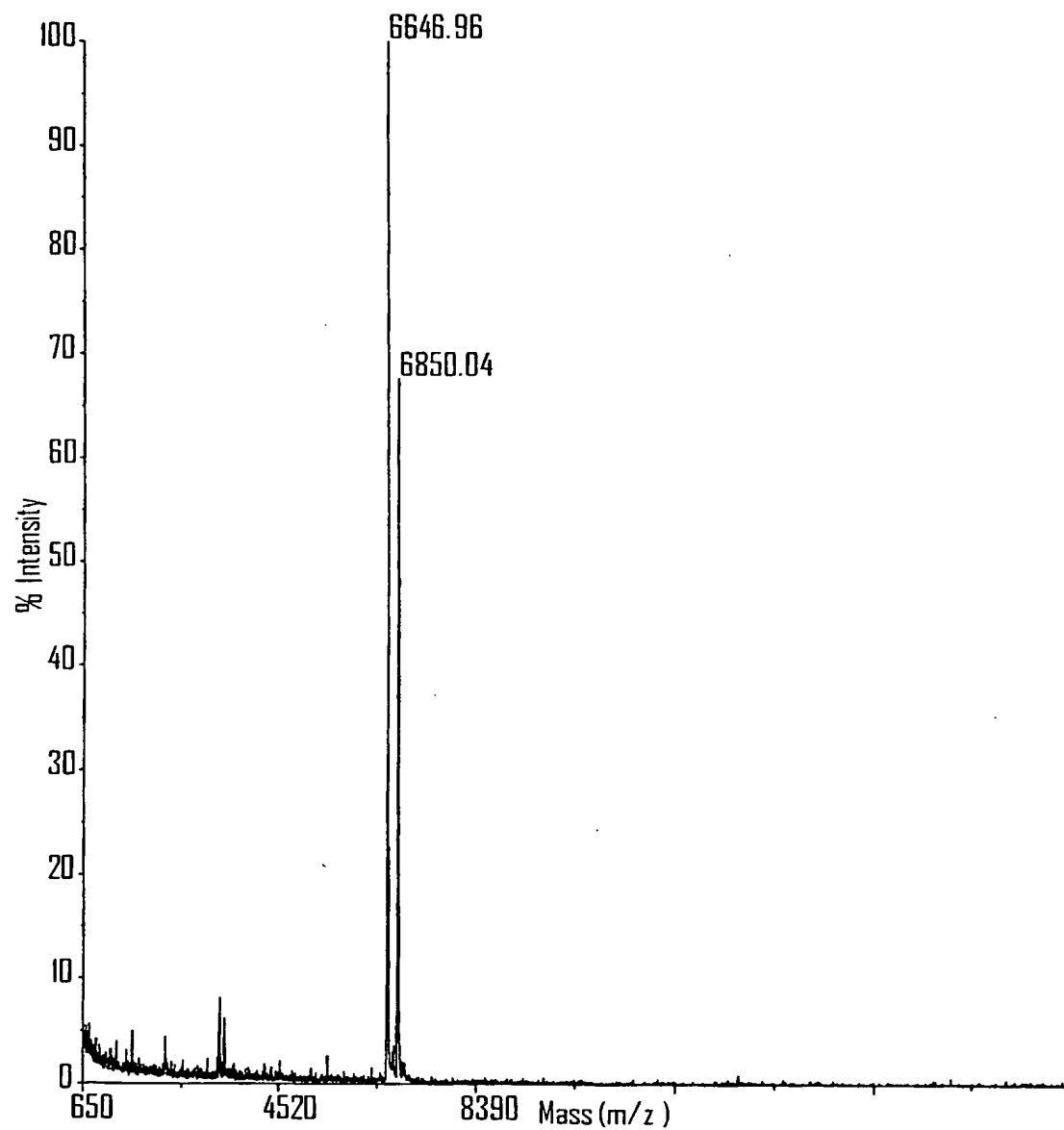
Figure 2

Figure 3

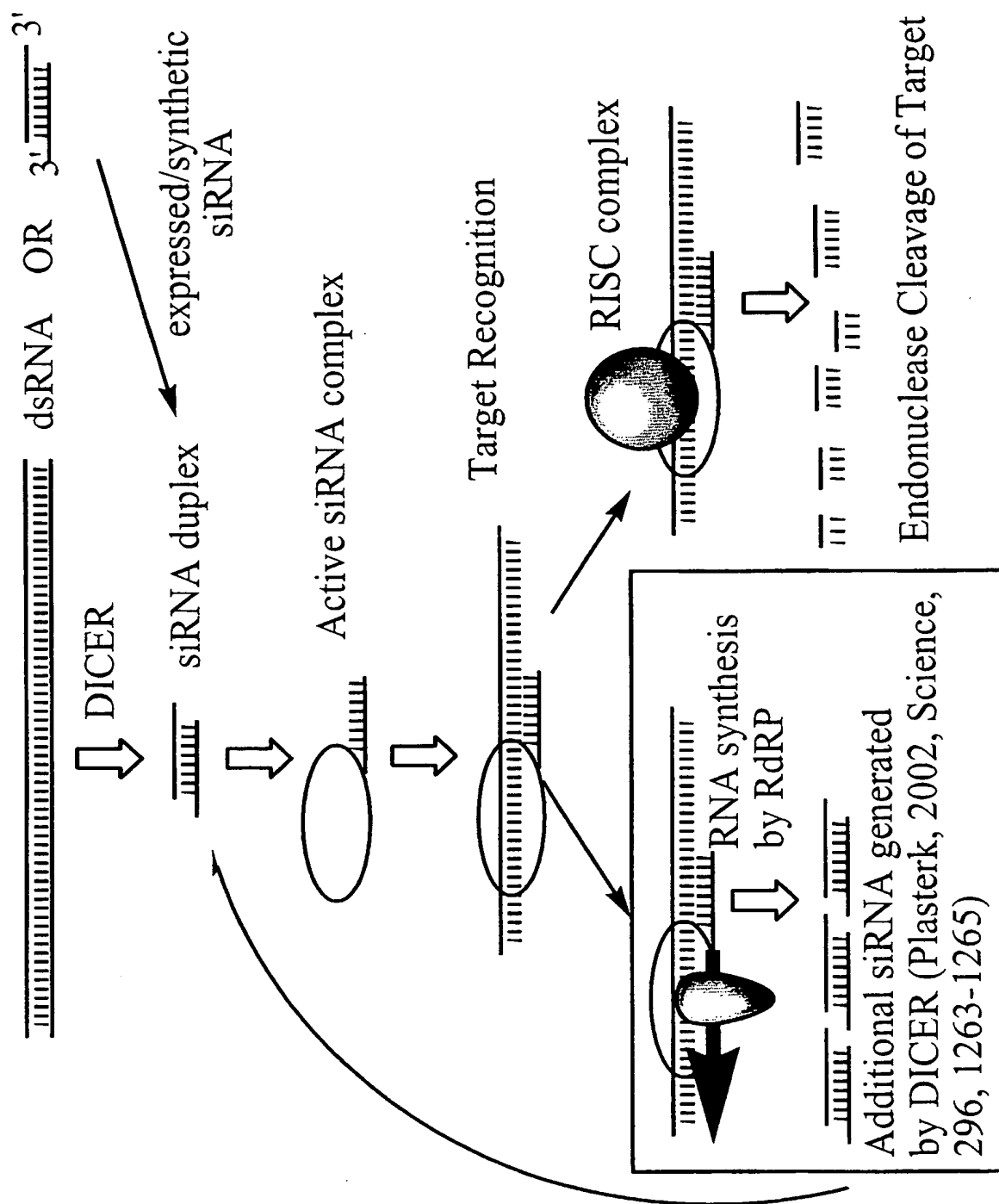
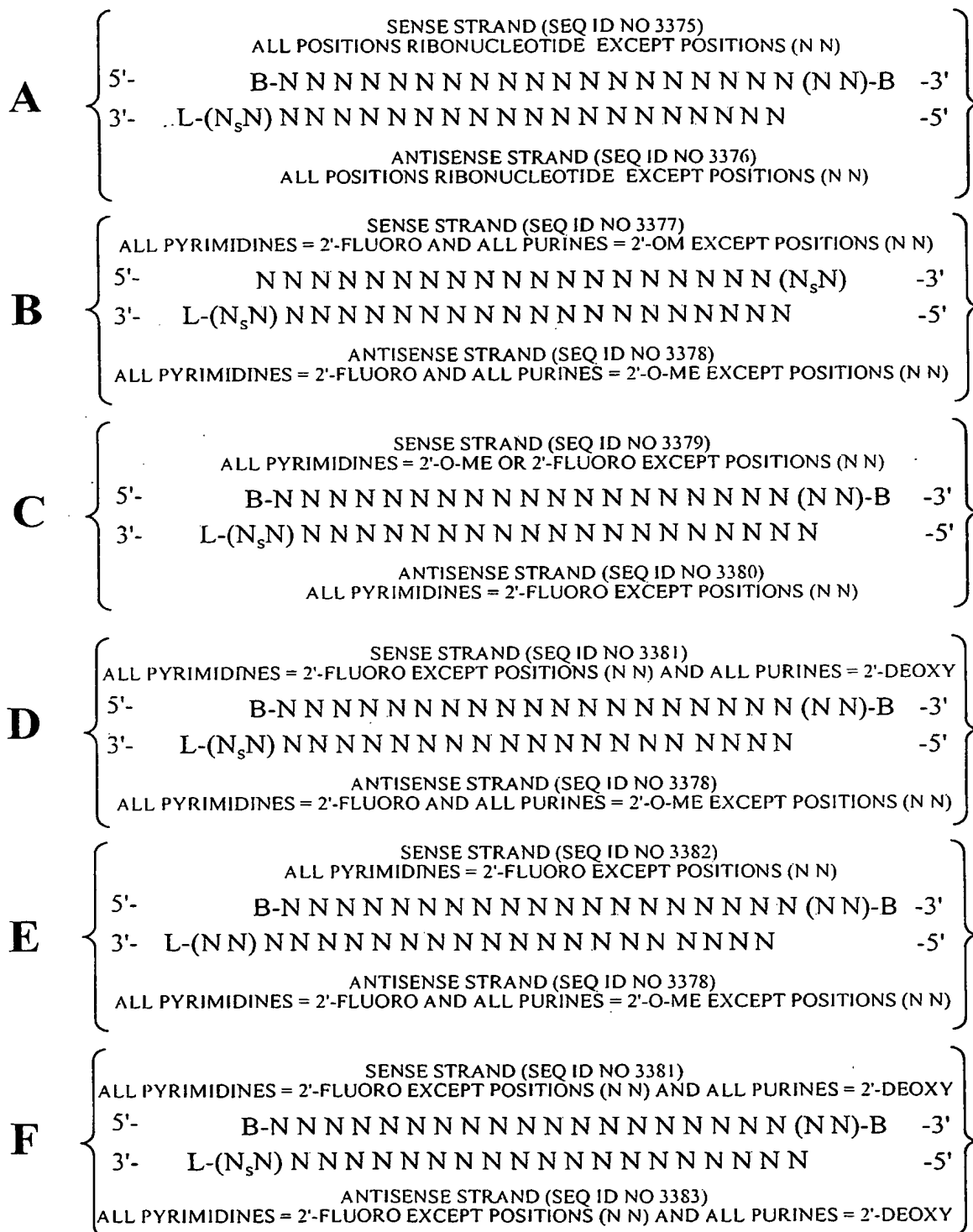
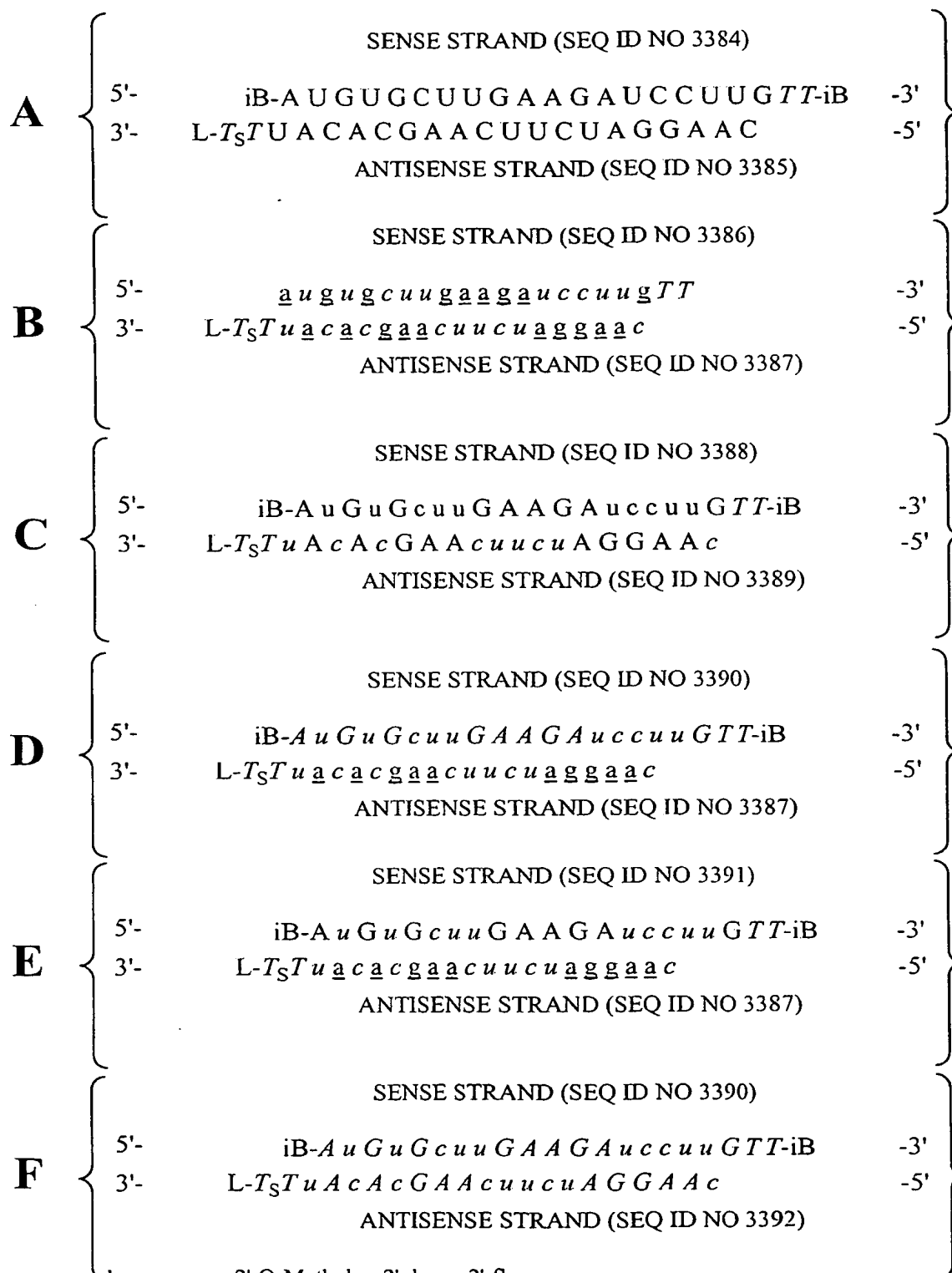


Figure 4

POSITIONS (NN) CAN COMPRISE ANY NUCLEOTIDE, SUCH AS DEOXYNUCLEOTIDES (eg. THYMIDINE) OR UNIVERSAL BASES B = ABASIC, INVERTED ABASIC, INVERTED NUCLEOTIDE OR OTHER TERMINAL CAP THAT IS OPTIONALLY PRESENTL = GLYCERYL or B THAT IS OPTIONALLY PRESENTS = PHOSPHOROTHIOATE OR PHOSPHORODITHIOATE that is optionally absent

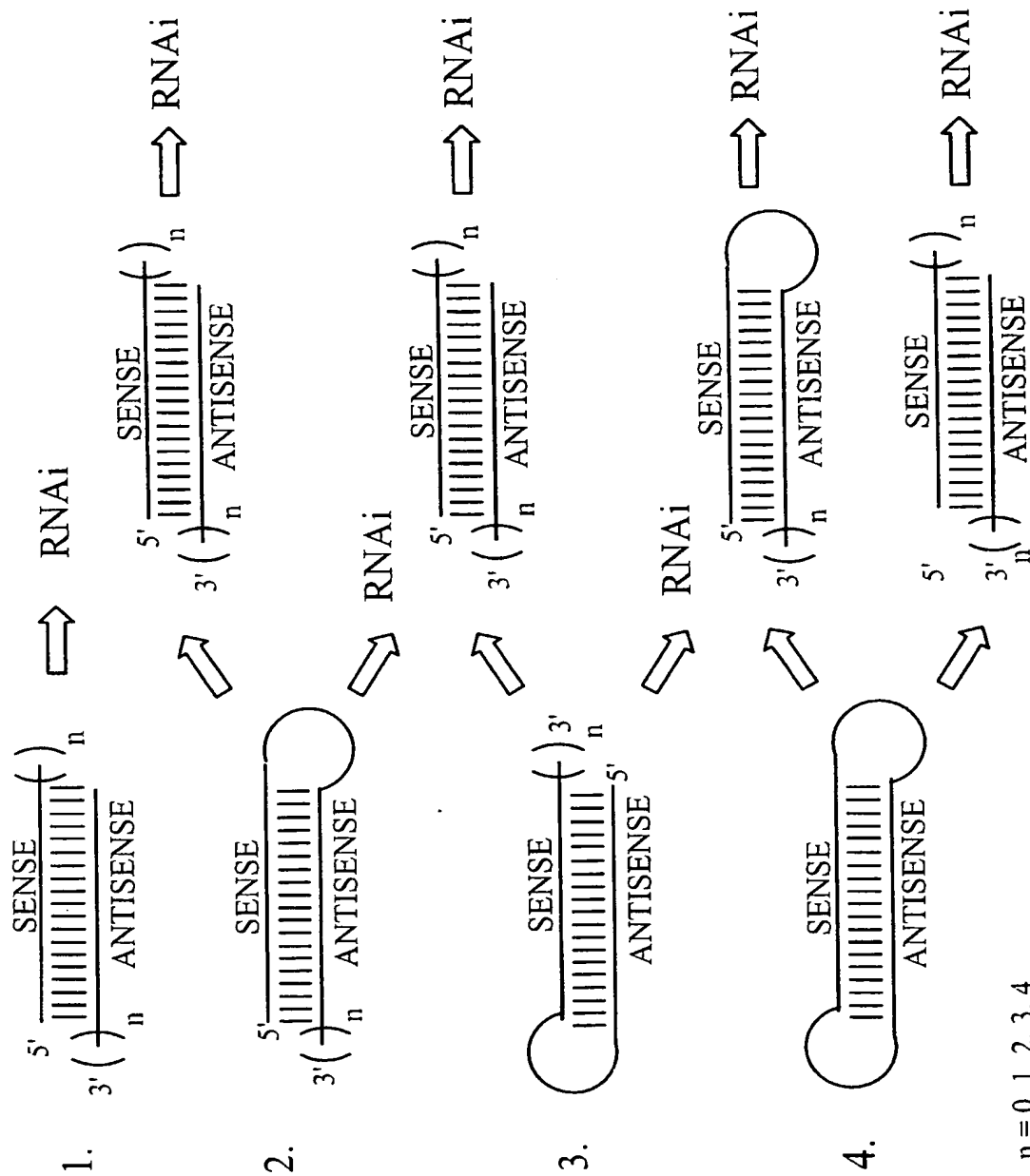
Figure 5

lower case = 2'-O-Methyl or 2'-deoxy-2'-fluoro

italic lower case = 2'-deoxy-2'-fluorounderline = 2'-O-methyl

ITALIC UPPER CASE = DEOXYIB = INVERTED
 DEOXYABASICL = GLYCERYL MOIETY or iB
 OPTIONALLY PRESENTS = PHOSPHOROTHIOATE (C
 PHOSPHORODITHIOATE OPTIONALLY PRESEN

Figure 6



[illegible]

Figure 9: Target site Selection using siRNA

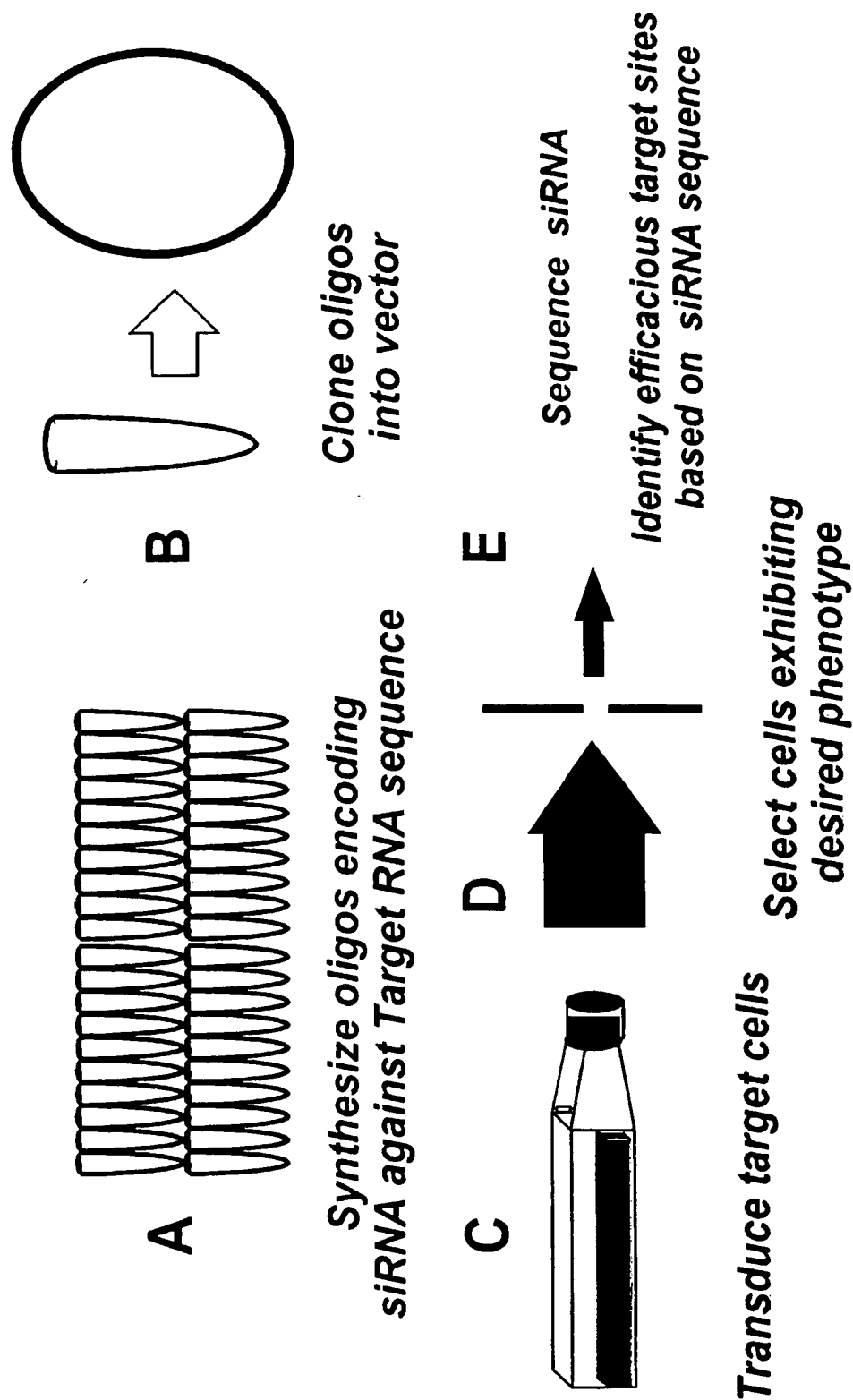
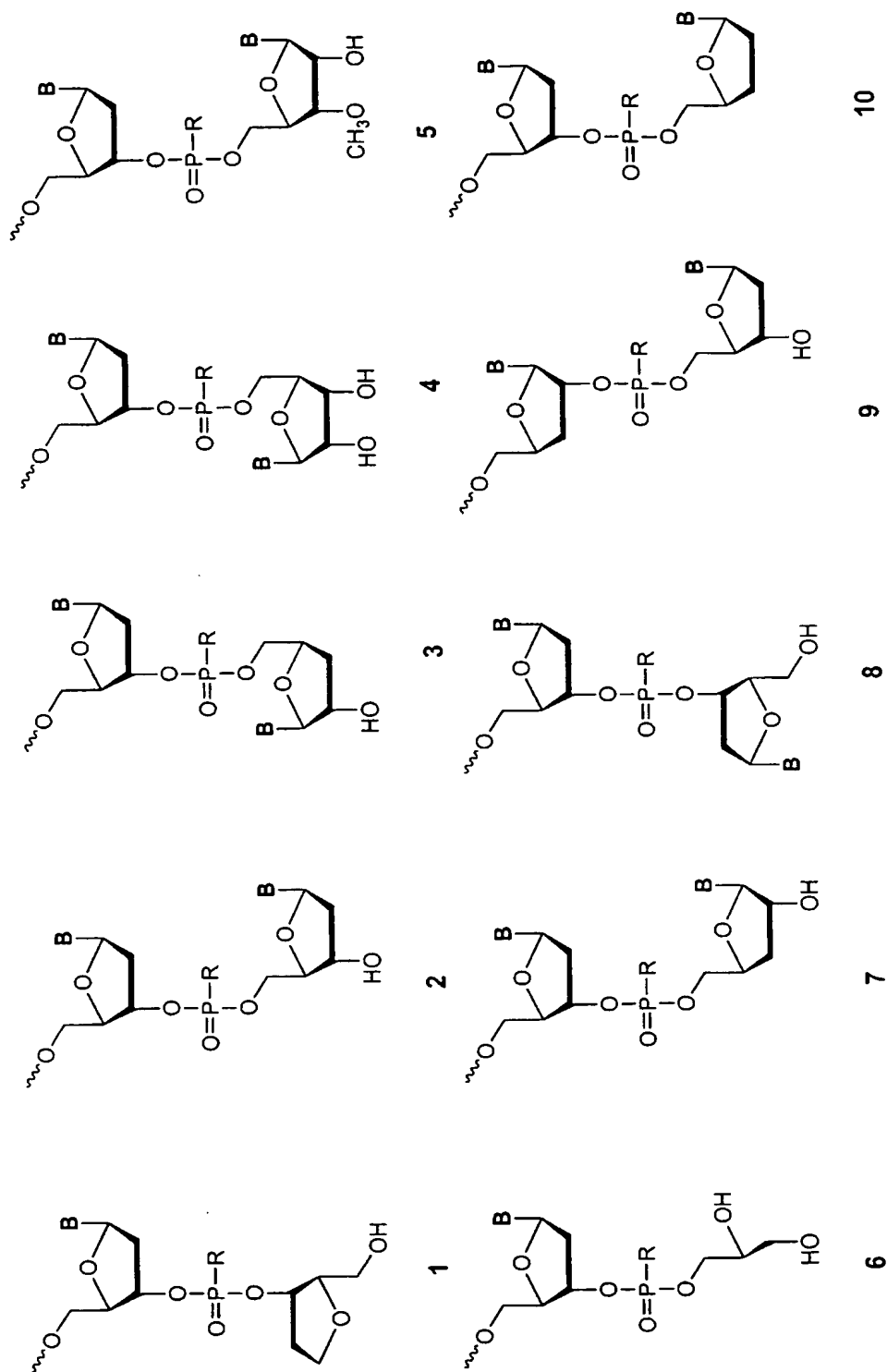


Figure 10

R = O, S, N, alkyl, substituted alkyl, O-alkyl, S-alkyl, alkaryl, or aralkyl
B = Independently any nucleotide base, either naturally occurring or chemically modified, or optionally H (abasic).

Figure 11: Modification Strategy

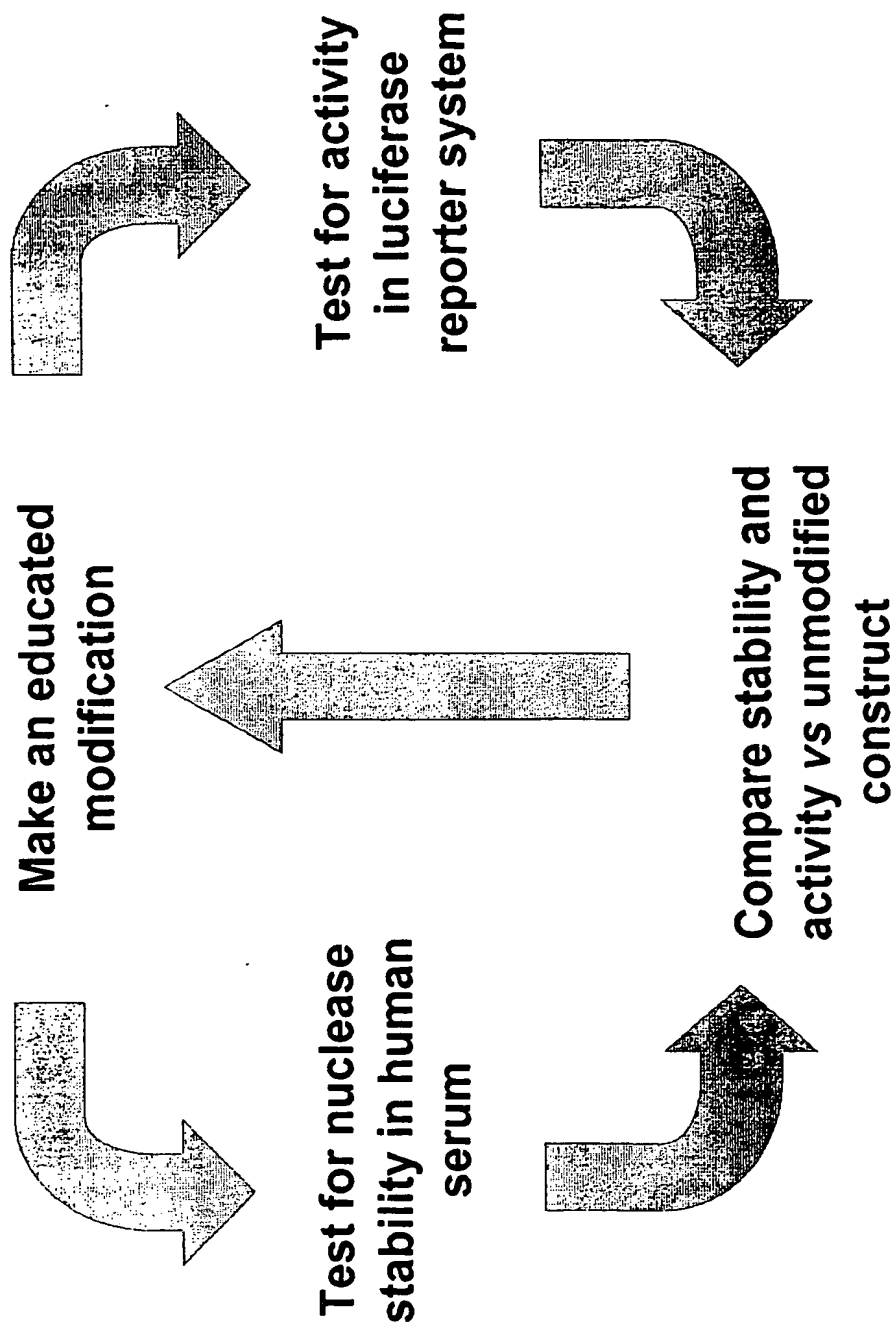


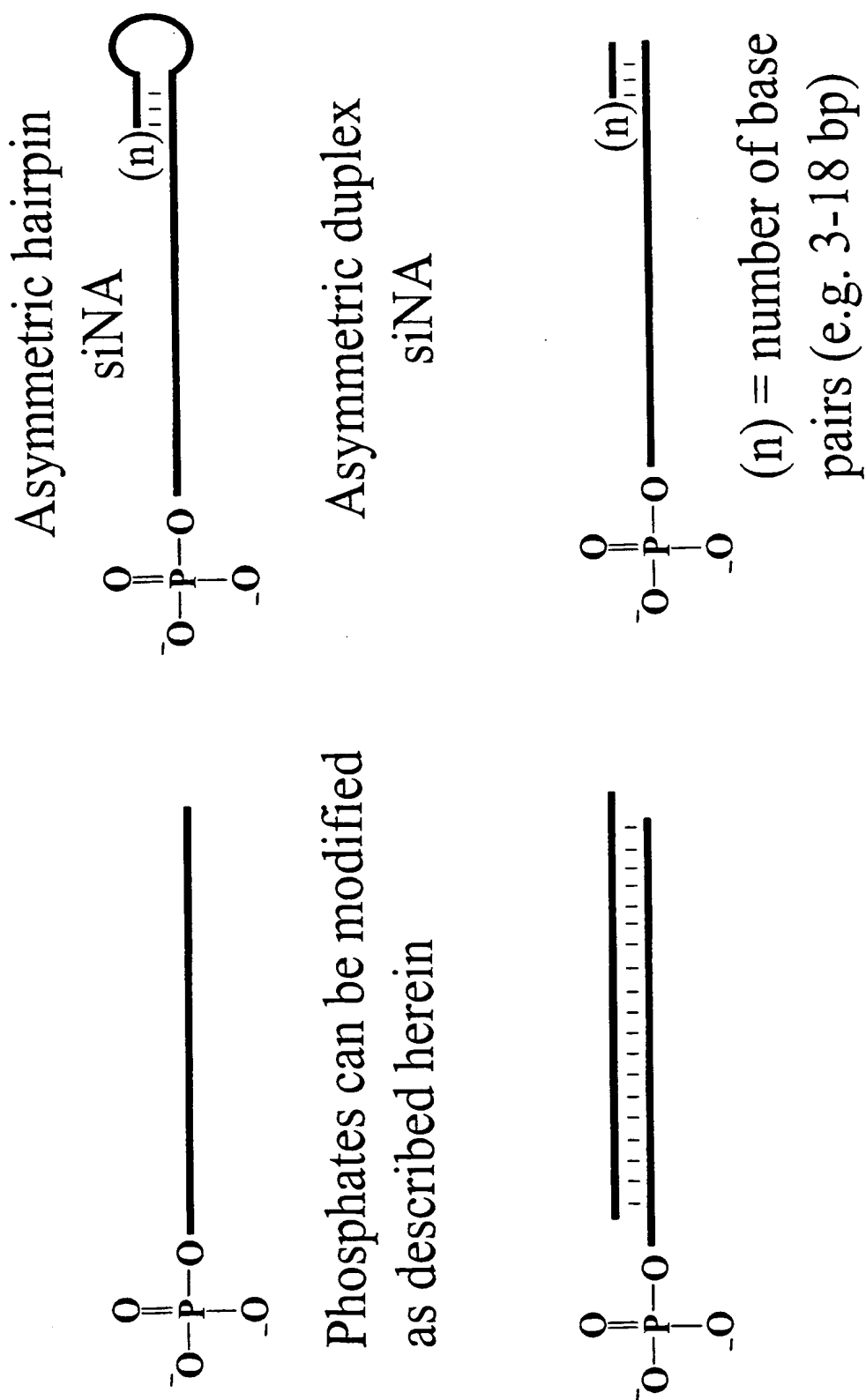
Figure 12: Phosphorylated siNA constructs

Figure 13: 5'-phosphate modifications

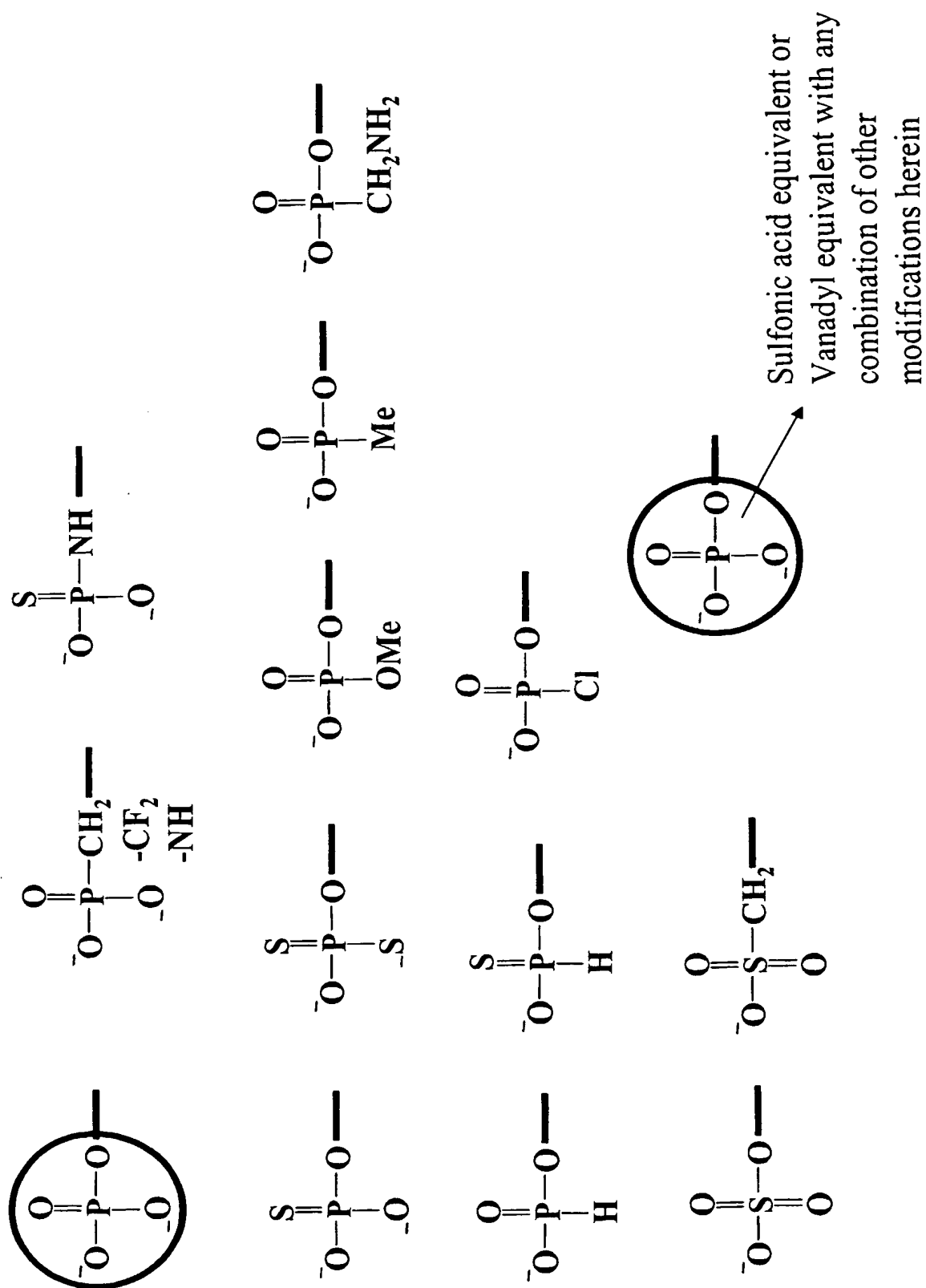


Figure 14A: Duplex forming oligonucleotide constructs that utilize palindrome or repeat sequences

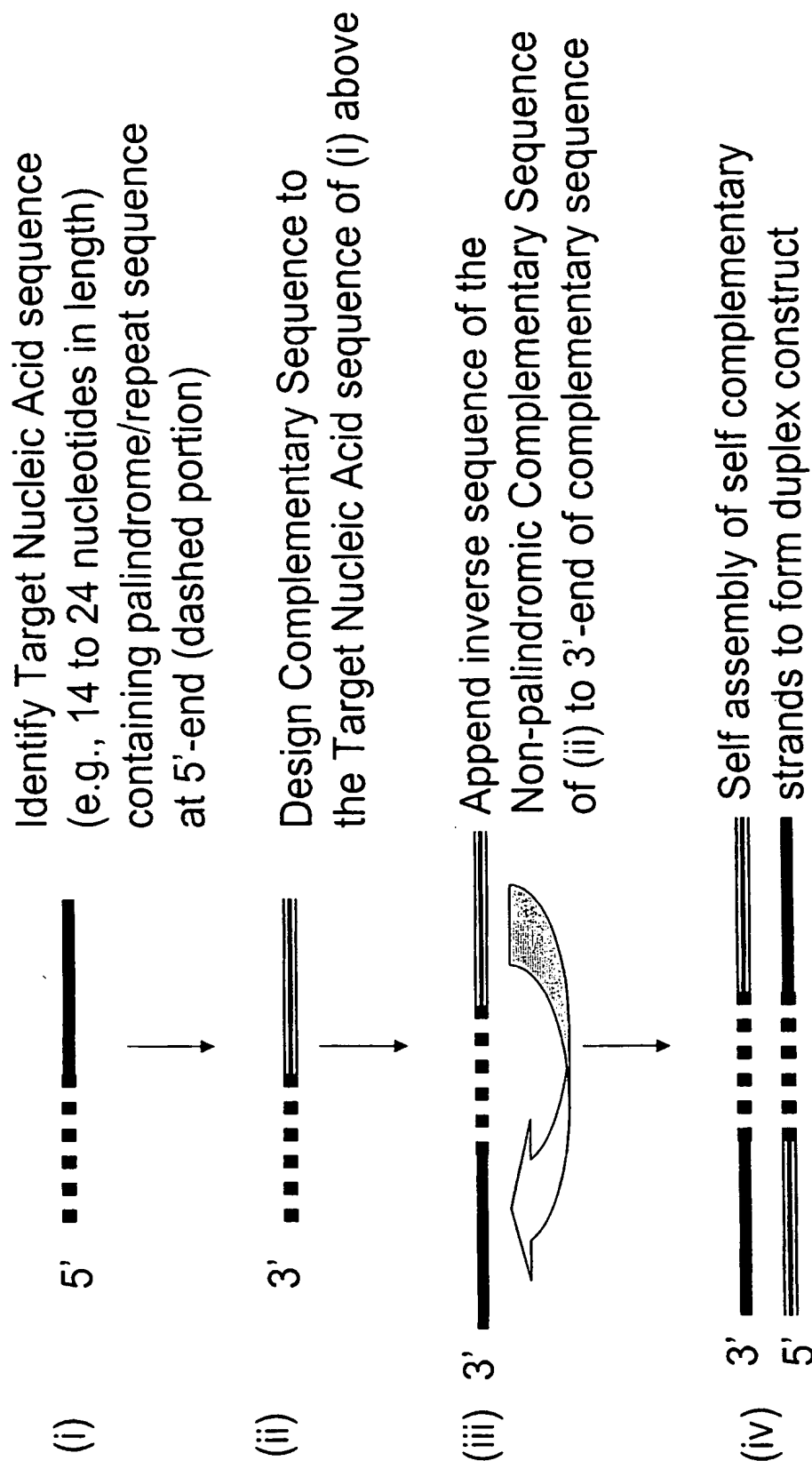


Figure 14B: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence

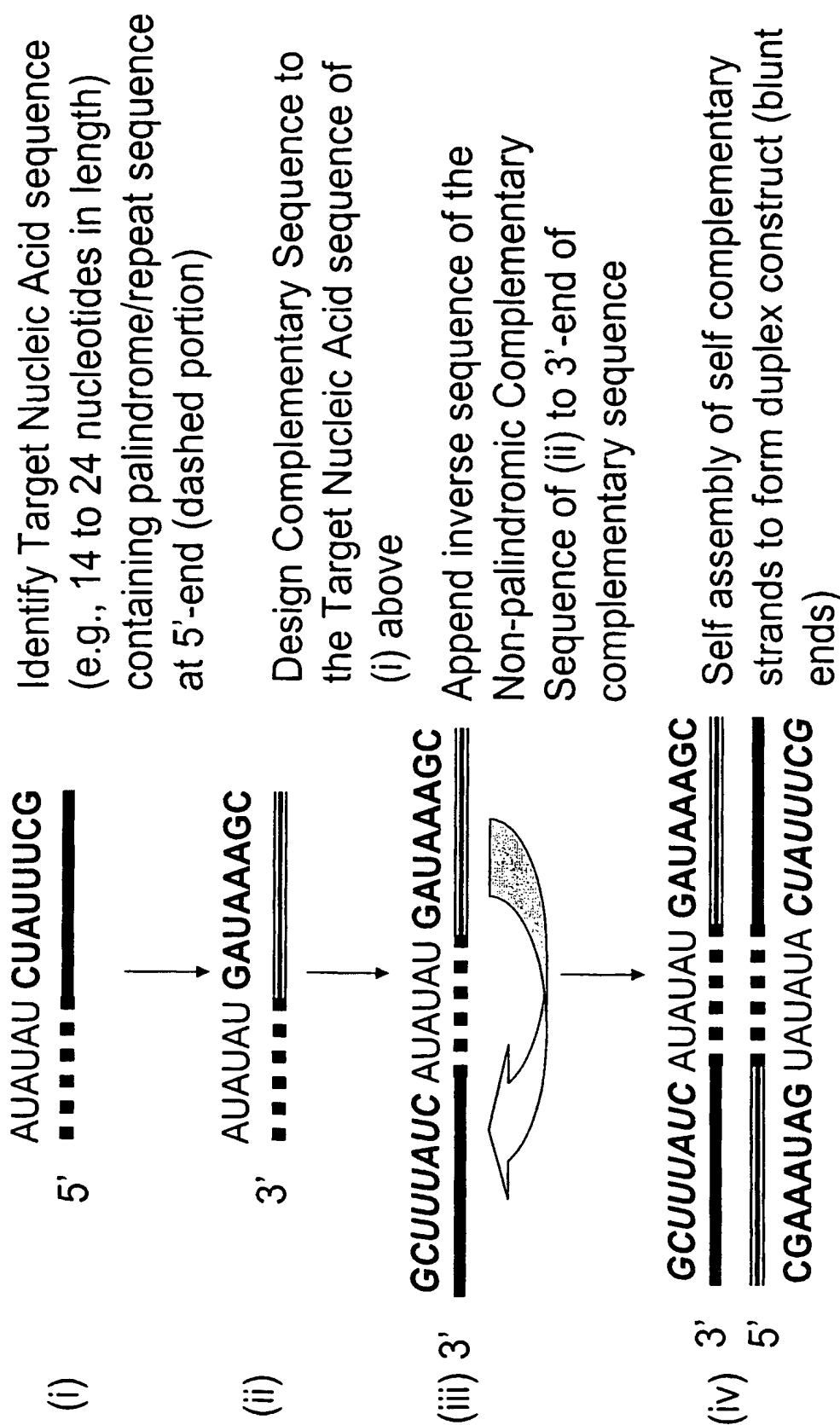


Figure 14C: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly

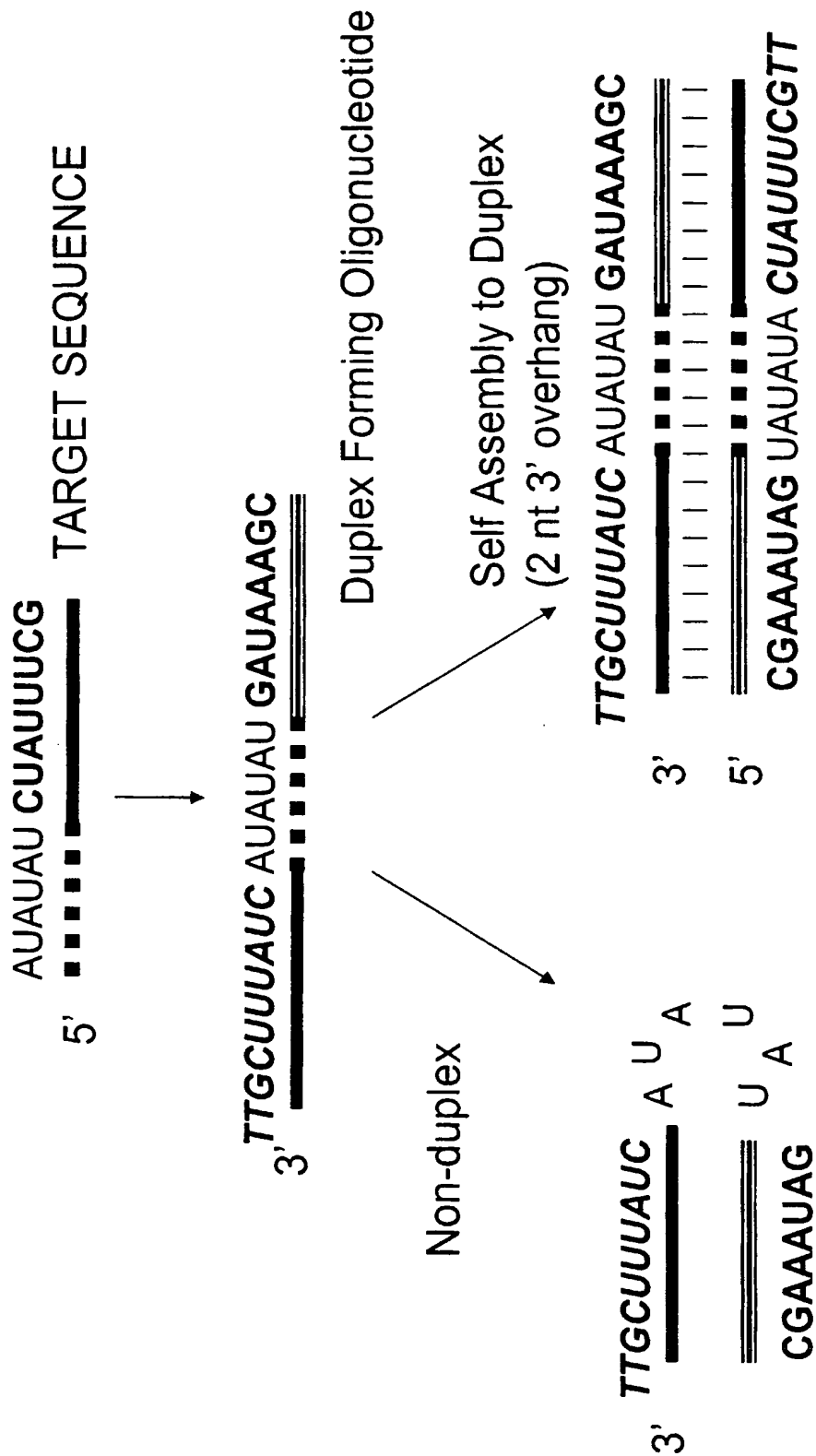


Figure 14D: Example of a duplex forming oligonucleotide sequence that utilizes a palindrome or repeat sequence, self assembly and inhibition of Target Sequence Expression

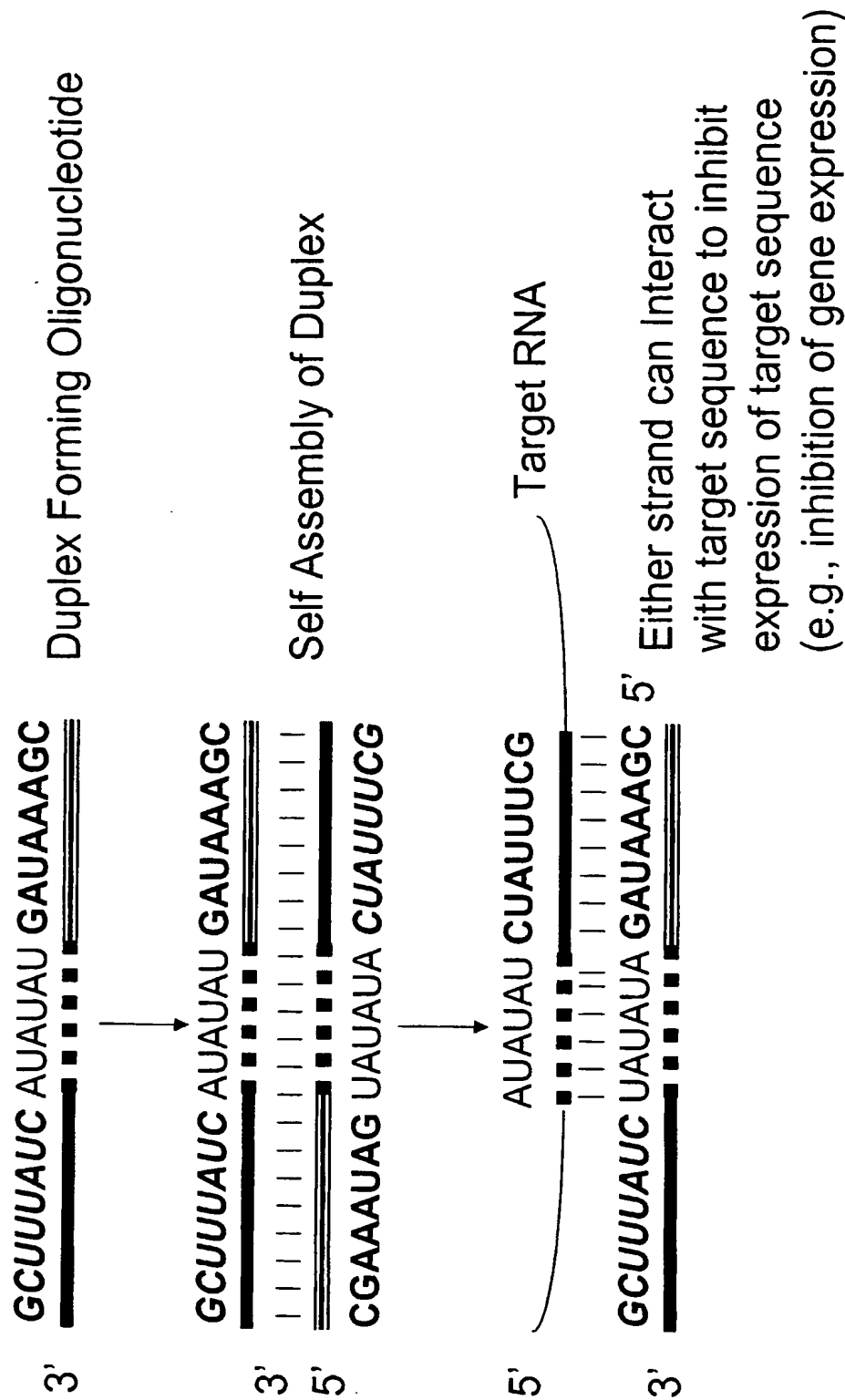


Figure 15: Duplex forming oligonucleotide constructs that utilize artificial palindrome or repeat sequences

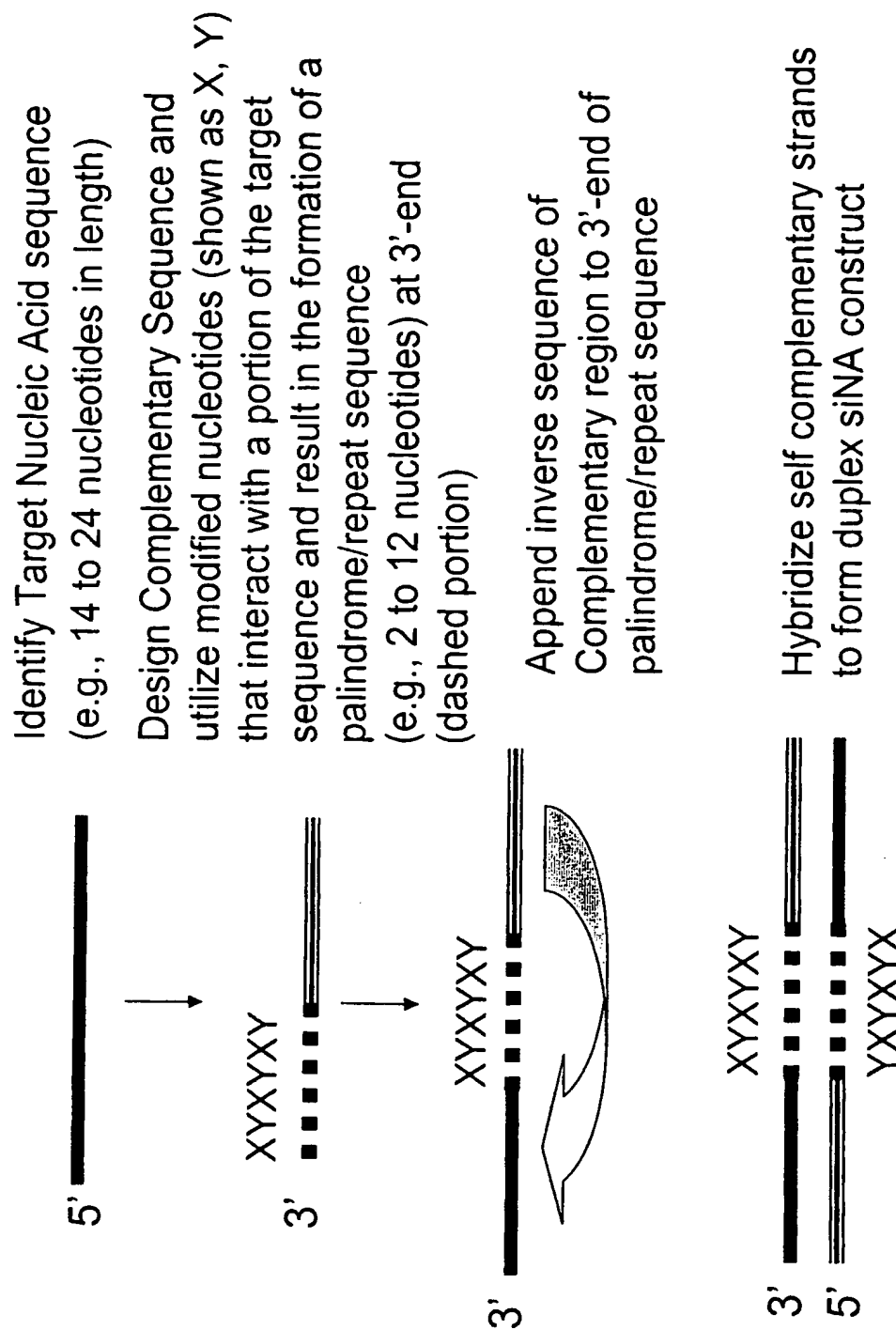


Figure 16: Examples of double stranded multifunctional siNA constructs with distinct complementary regions

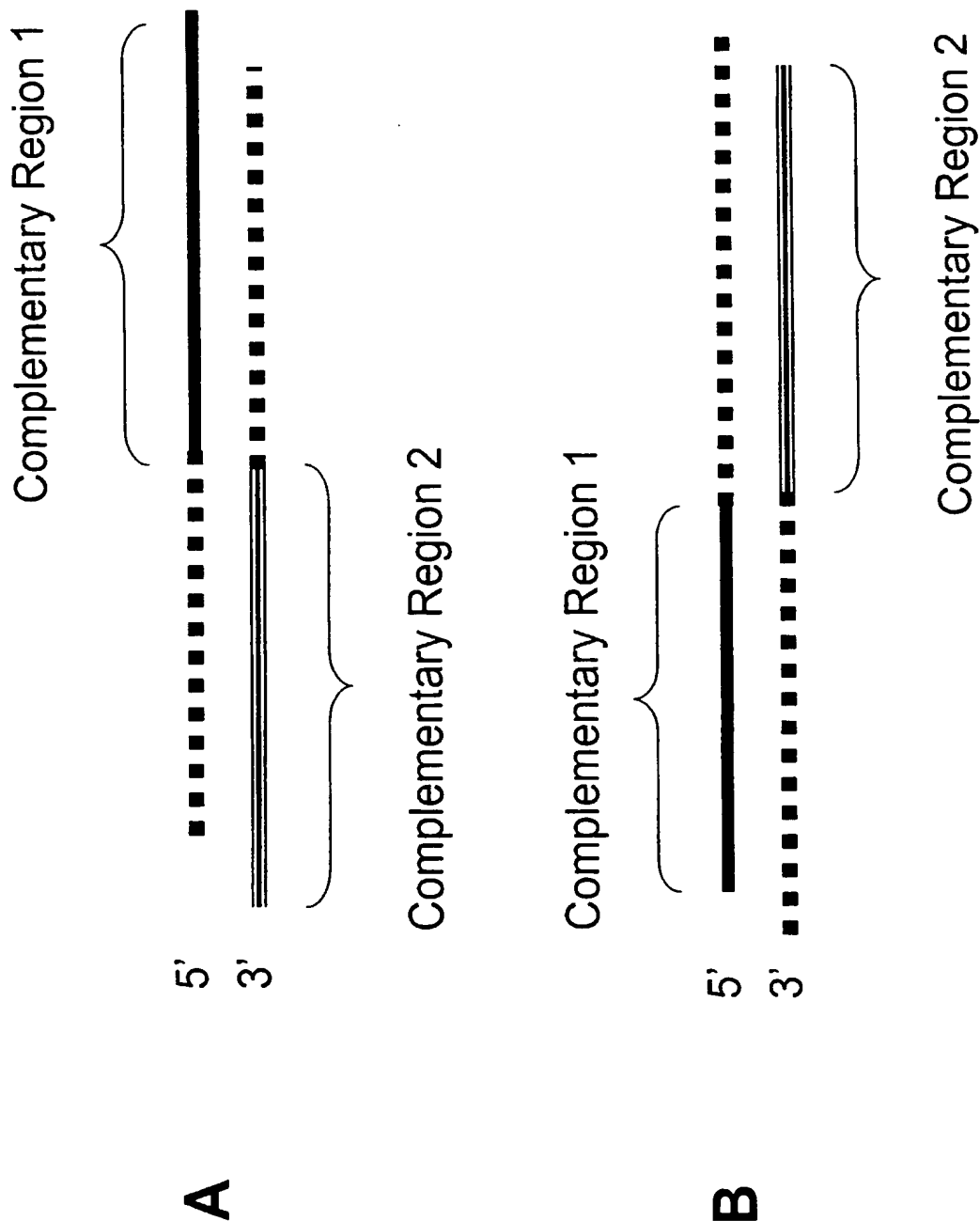


Figure 17: Examples of hairpin multifunctional siNA constructs with distinct complementary regions

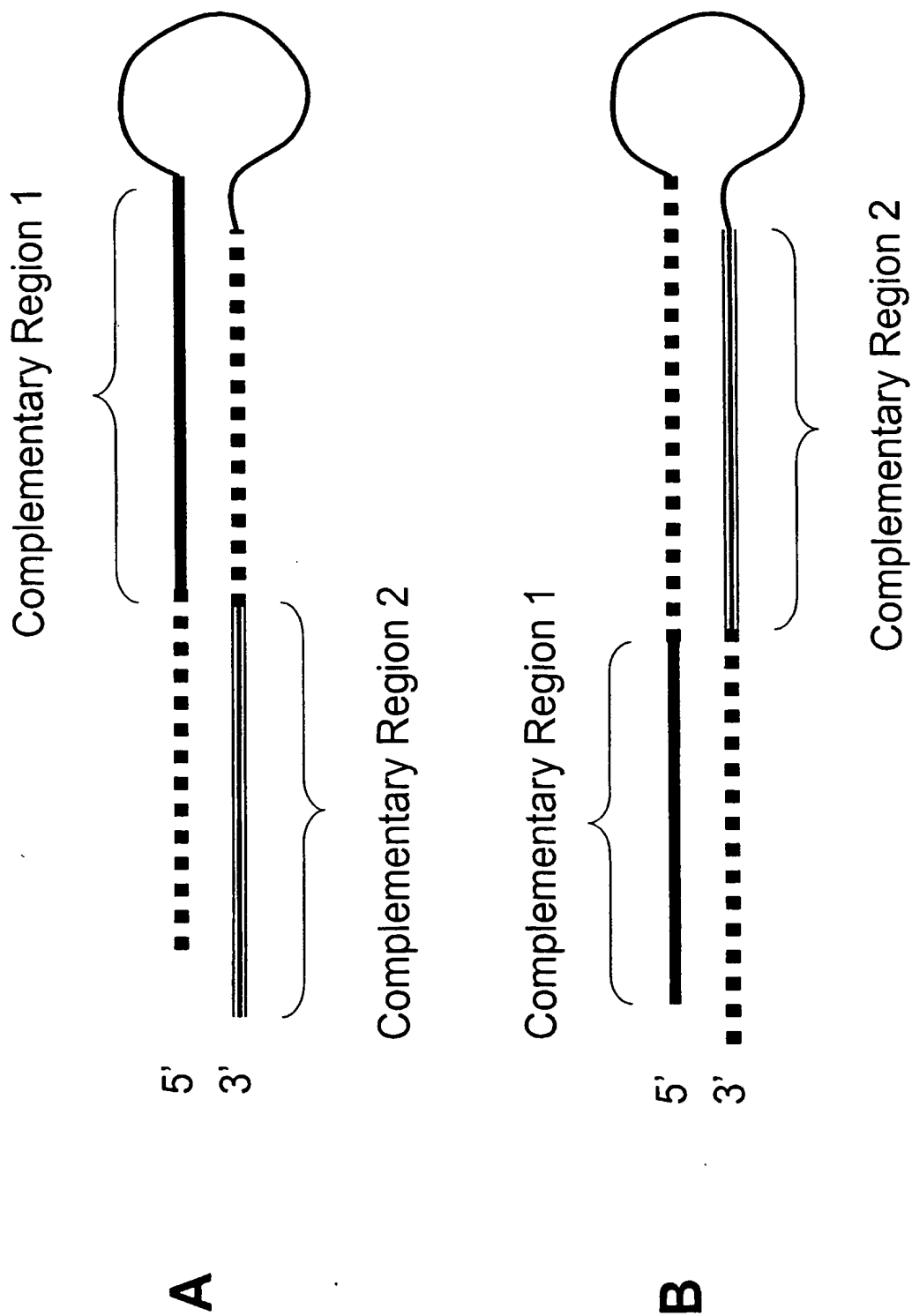


Figure 18: Examples of double stranded multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region

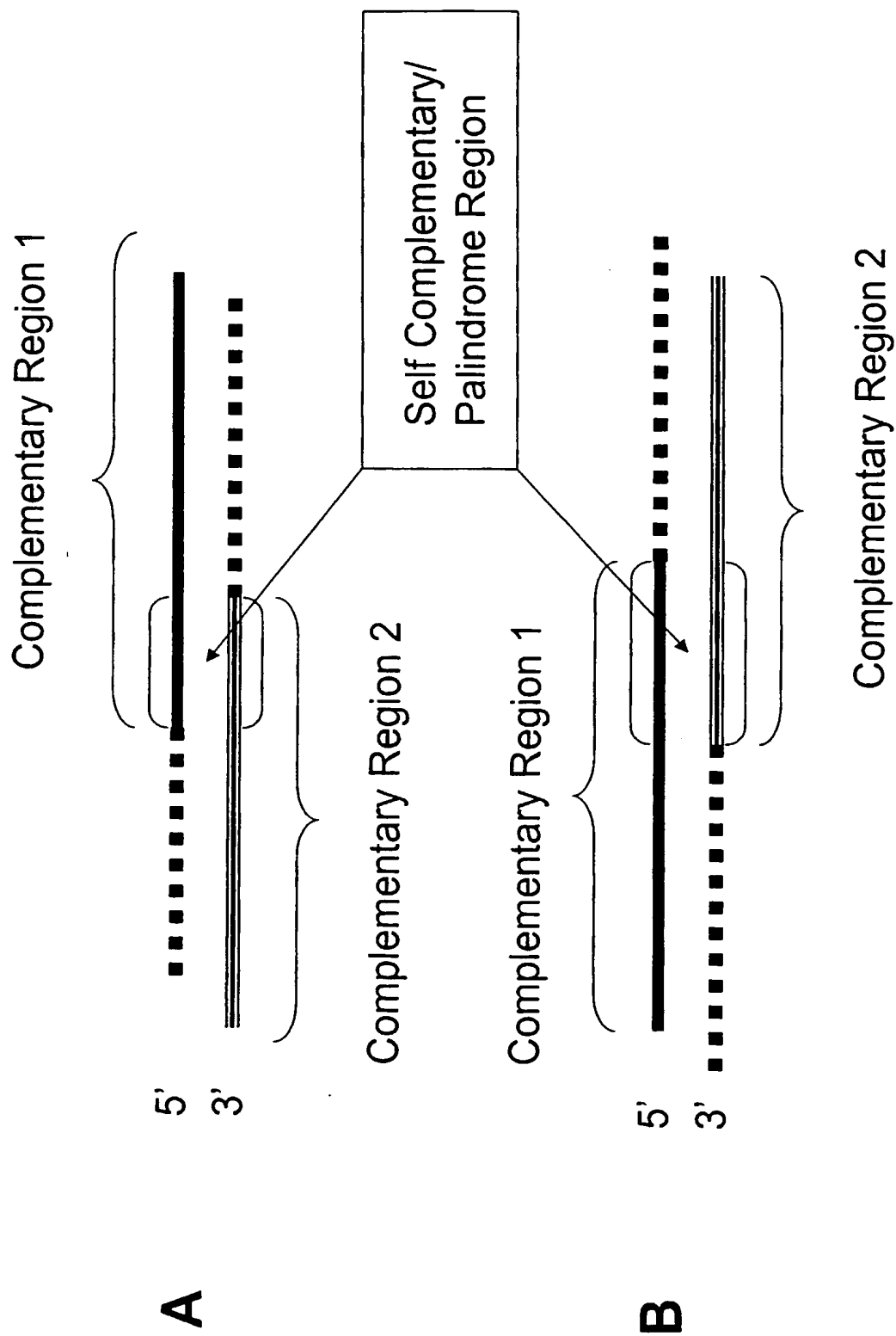
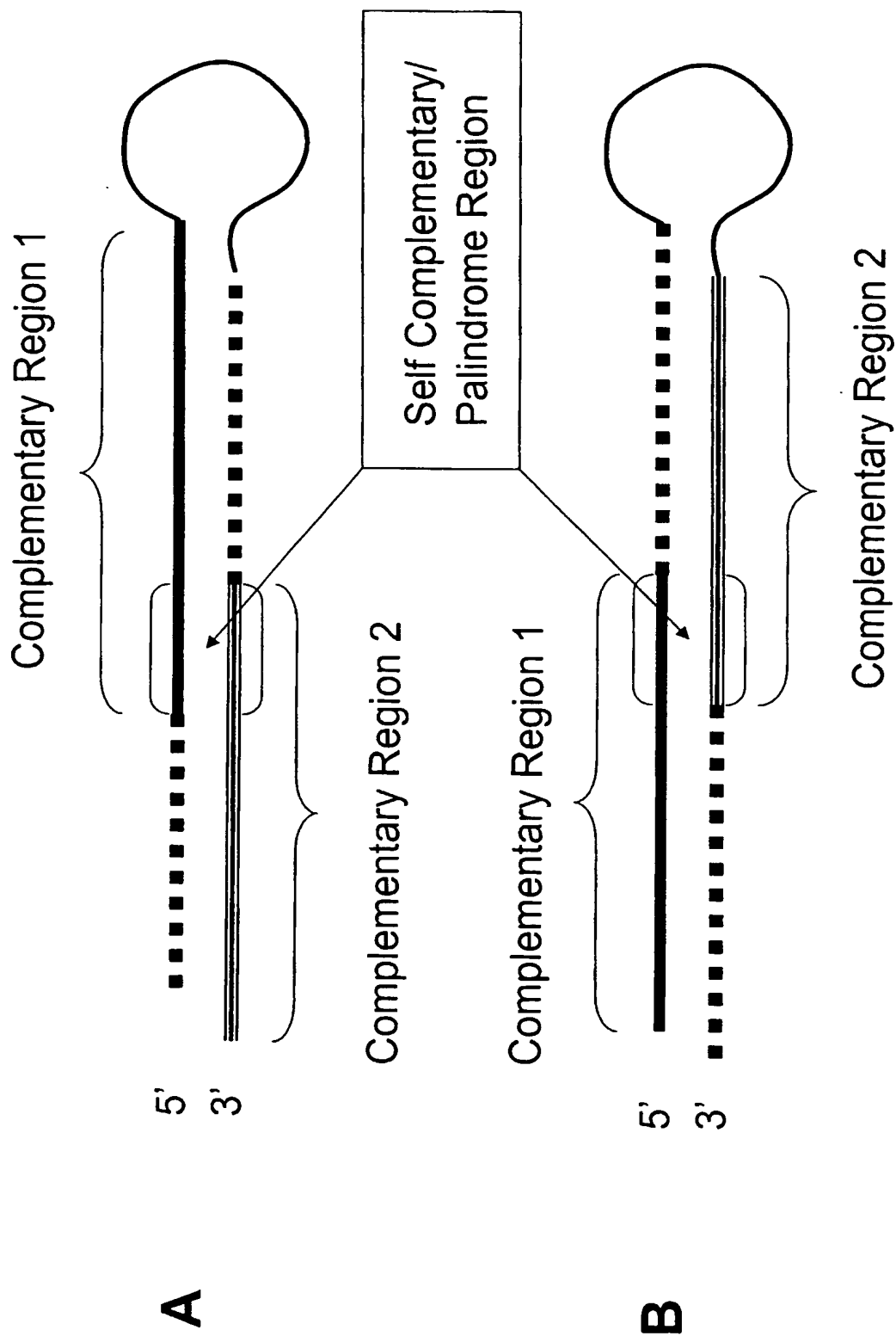


Figure 19: Examples of hairpin multifunctional siNA constructs with distinct complementary regions and a self complementary/palindrome region



**Figure 20: Example of multifunctional siNA targeting two separate
Target nucleic acid sequences**

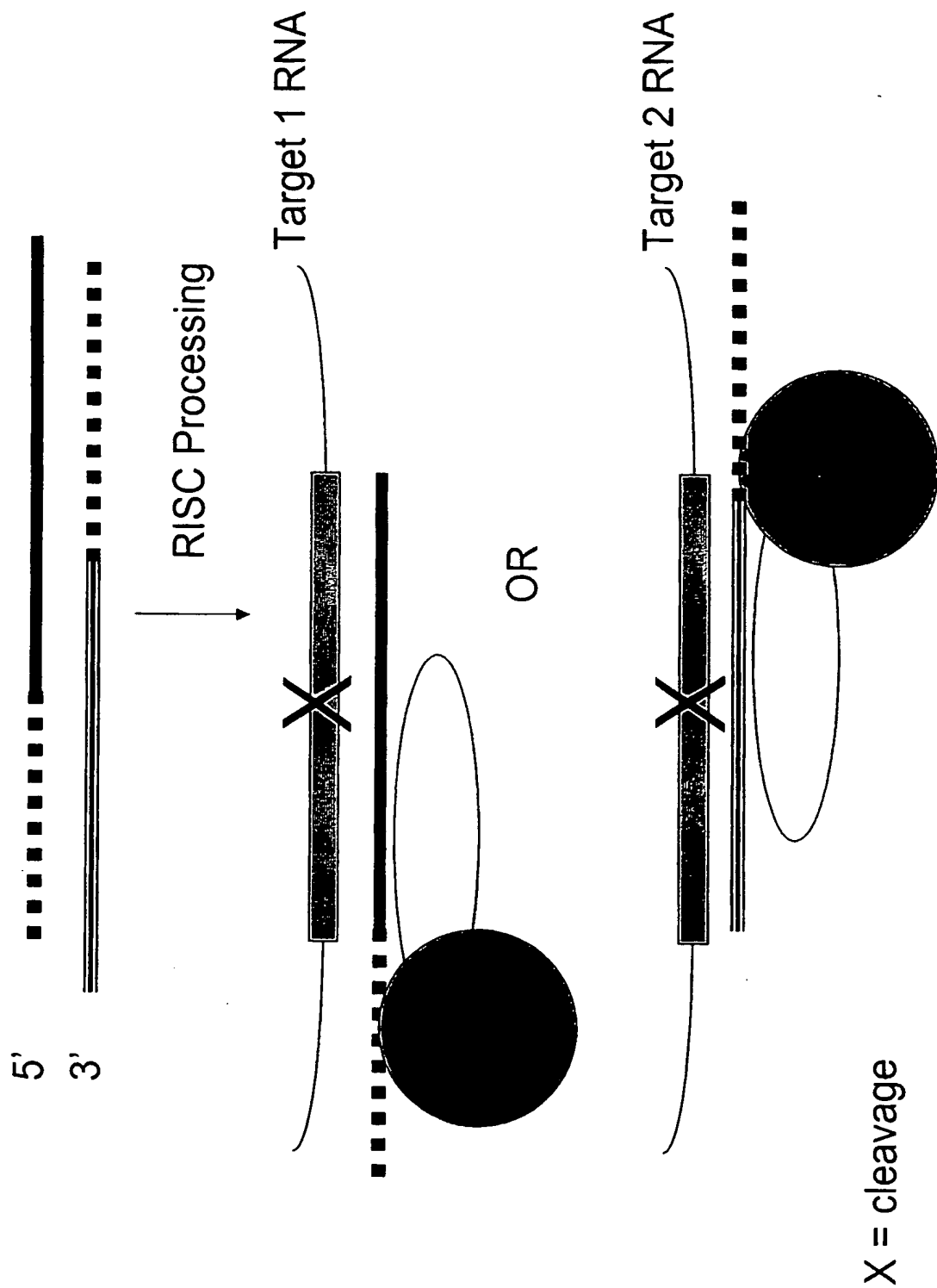


Figure 21: Example of multifunctional siNA targeting two regions within the same target nucleic acid sequence

